4. Birnbaum G, *et al.* Combining beta interferon and atorvastatin may increase disease activity in multiple sclerosis. *Neurology* 2008; 71: 1390–5.
5. Rudick RA, *et al.* Effect of statins on clinical and molecular responses to intramuscular interferon beta-1a. *Neurology* 2009; 72: 1989–93.

Organ and tissue transplantation. Cardiovascular disease is an important cause of morbidity and mortality after organ transplantation and statins are useful for cardiovascular risk reduction in these patients. They may also have immunomodulatory effects and have reduced the risk of rejection in some studies.[1] Some evidence also suggests that they may reduce the risk of sepsis and post-transplantation infections.[2] A meta-analysis of patients who had undergone heart transplantation (p. 1938.2) considered that treatment with a statin within 3 months of transplantation reduced allograft rejection with haemodynamic compromise and reduced 1-year mortality;[3] it was calculated that one life was saved for every 8.5 treated heart transplant patients. There is some tentative evidence that statin therapy may also reduce acute rejection and the development of obliterative bronchiolitis in patients who have undergone lung transplantation (p. 1941.3),[4] although prospective controlled studies are lacking.

1. Paraskevas KI. Applications of statins in cardiothoracic surgery: more than just lipid-lowering. *Eur J Cardiothorac Surg* 2008; 33: 377–90.
2. Sun H-Y, Singh N. Antimicrobial and immunomodulatory attributes of statins: relevance in solid-organ transplant recipients. *Clin Infect Dis* 2009; 48: 745–55.
3. Mehra MR, Raval NY. Metaanalysis of statins and survival in de novo cardiac transplantation. *Transplant Proc* 2004; 36: 1539–41.
4. Johnson BA, *et al.* Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003; 167: 1271–8.

Osteoporosis. Statins appear to have effects on bone metabolism and preliminary studies[1,2] have suggested that some statins may increase bone mineral density. However, the clinical relevance of any effect is unclear.[3] Several case-control studies[4–6] have also suggested that use of statins may protect against fractures, but another case-control study[7] and an observational study[8] failed to support such an association. A review[9] of 4 further observational studies found that the risk of fracture was lower in women taking statins, but analysis of data from randomised studies of statins for cardiovascular disease[10,11] failed to confirm any effect, and controlled studies are needed[3,12] to confirm the role of statins in the management of osteoporosis (p. 1168.1).

1. Edwards CJ, *et al.* Oral statins and increased bone-mineral density in postmenopausal women. *Lancet* 2000; 355: 2218–9.
2. Watanabe S, *et al.* Effects of 1-year treatment with fluvastatin or pravastatin on bone. *Am J Med* 2001; 110: 584–7.
3. Jadhav SB, Jain GK. Statins and osteoporosis: new role for old drugs. *J Pharm Pharmacol* 2006; 58: 3–18.
4. Chan KA, *et al.* Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2000; 355: 2185–8.
5. Meier CR, *et al.* HMG-CoA reductase inhibitors and the risk of fractures. *JAMA* 2000; 283: 3205–10.
6. Wang PS, *et al.* HMG-CoA reductase inhibitors and the risk of hip fractures in elderly patients. *JAMA* 2000; 283: 3211–16.
7. van Staa T-P, *et al.* Use of statins and risk of fractures. *JAMA* 2001; 285: 1850–55. Correction. *ibid.*; 286: 674.
8. LaCroix AZ, *et al.* Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med* 2003; 139: 97–104.
9. Bauer DC, *et al.* Use of statins and fracture: results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials. *Arch Intern Med* 2004; 164: 146–52.
10. Reid IR, *et al.* Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. *Lancet* 2001; 357: 509–12.
11. Pedersen TR, Kjekshus J. 4S Study Group. Statin drugs and the risk of fracture. *JAMA* 2000; 284: 1921–2.
12. Coons JC. Hydroxymethylglutaryl-coenzyme A reductase inhibitors in osteoporosis management. *Ann Pharmacother* 2002; 36: 326–30.

Adverse Effects

The commonest adverse effects of therapy with simvastatin and other statins are gastrointestinal disturbances. Other adverse effects are generally rare but include headache, rash, dizziness, insomnia, hyperglycaemia and diabetes mellitus, peripheral neuropathy, reversible cognitive impairment, depression, interstitial lung disease, sexual dysfunction, and alopecia. Hypersensitivity reactions have occurred, including anaphylaxis, angioedema, urticaria, photosensitivity, fever, flushing, dyspnoea, thrombocytopenia, toxic epidermal necrolysis, dermatomyositis, vasculitis, and lupus-like syndrome. Reversible increases in serum-transaminase concentrations may occur. Hepatitis, hepatic failure, and pancreatitis have been reported. Dose-related myopathy, characterised by myalgia and muscle weakness and associated with increased creatine phosphokinase concentrations, has been reported. Drug interactions may increase the risk of myopathy, see Interactions, p. 1494.2. Rarely, rhabdomyolysis with acute renal failure may develop.

General references.

1. Farmer JA, Torre-Amione G. Comparative tolerability of the HMG-CoA reductase inhibitors. *Drug Safety* 2000; 23: 197–213.
2. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. *Drugs* 2001; 61: 197–206.
3. Pasternak RC, *et al.* ACC/AHA/NHLBI clinical advisory on the use and safety of statins. *Circulation* 2002; 106: 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 29/05/08)
4. Karthikeyan VJ. Adverse effects of statins: an update. *Adverse Drug React Bull* 2005; (Aug): 895–8.
5. McKenney JM, *et al.* Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. *Am J Cardiol* 2006; 97(Issue 8 suppl 1): 89C–94C.
6. Armitage J. The safety of statins in clinical practice. *Lancet* 2007; 370: 1781–90.
7. Brown WV. Safety of statins. *Curr Opin Lipidol* 2008; 19: 558–62.
8. Beltowski J, *et al.* Adverse effects of statins–mechanisms and consequences. *Curr Drug Saf* 2009; 4: 209–28.
9. Naci H, *et al.* Comparative tolerability and harms of individual statins: a study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. *Circ Cardiovasc Qual Outcomes* 2013; 6: 390–9.

Incidence of adverse effects. By February 1992 the UK CSM had received 738 reports of adverse effects associated with simvastatin,[1] from an estimated 257 000 prescriptions. Abnormal hepatic function and myalgia were 2 of the most frequently reported reactions, with 36 and 48 reports respectively, including 5 reports of hepatitis and 2 of jaundice. Other muscle effects included 3 reports of myositis, 10 of myopathy, and 7 reports of asymptomatic increases in serum creatine kinase concentrations. Gastrointestinal adverse effects accounted for 20% of the reports; skin, neurological and musculoskeletal effects for 15% each; psychiatric effects for 10%; liver effects for 7%; and visual effects for 4%. A systematic review[2] of data from clinical studies confirmed that the risk of liver transaminase elevation was increased by statins but there was no significant increase in the incidence of myalgia (reported in about 15% of patients), creatine kinase elevation (0.9%), or rhabdomyolysis (0.2%), compared with placebo. The incidence of adverse effects may be greater with high-dose therapy.[3,4]

1. CSM. Simvastatin. *Current Problems* 33 1992. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024451&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Kashani A, *et al.* Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006; 114: 2788–97.
3. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol* 2007; 49: 1753–62.
4. Silva M, *et al.* Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. *Clin Ther* 2007; 29: 253–60.

Carcinogenicity. For discussion of the effects of statins on the risk of cancer, see Malignant Neoplasms under Uses, p. 1491.3.

Effects on the blood. *Thrombocytopenia* has been reported rarely with statin therapy. Serious thrombocytopenic purpura has occurred with simvastatin, with the onset ranging from 1 or 2 days[1,2] to 11 or 12 months[3,4] after starting treatment. Platelet counts improved after stopping simvastatin in each case, although most patients were given corticosteroids, immunoglobulins, or plasma exchange. There has also been a similar report with atorvastatin,[5] which recurred on rechallenge; the patient had previously taken simvastatin without developing thrombocytopenia, suggesting an idiosyncratic reaction.

A case of *haemolytic anaemia* has been reported[6] in a patient taking lovastatin; no adverse effect was seen when the patient was given simvastatin.

Statins have effects on coagulation and fibrinolysis but these are generally beneficial (see Action under Uses, p. 1489.3); there have been rare reports of *ocular haemorrhage*,[7] but the association with statins is not established.

1. McCarthy LJ, *et al.* Thrombotic thrombocytopenic purpura and simvastatin. *Lancet* 1998; 352: 1284–5.
2. Sundram F, *et al.* Thrombotic thrombocytopenic purpura associated with statin treatment. *Postgrad Med J* 2004; 80: 551–2.
3. Possamai G, *et al.* Thrombocytopenic purpura during therapy with simvastatin. *Haematologica* 1992; 77: 357–8.
4. Groneberg DA, *et al.* Simvastatin-induced thrombocytopenia. *Am J Hematol* 2001; 67: 277.
5. González-Ponte ML, *et al.* Atorvastatin-induced severe thrombocytopenia. *Lancet* 1998; 352: 1284.
6. Robbins MJ, *et al.* Lovastatin-induced hemolytic anemia: not a class-specific reaction. *Am J Med* 1995; 99: 328–9.
7. Praunfelder FW. Ocular hemorrhage possibly the result of HMG-CoA reductase inhibitors. *J Ocul Pharmacol Ther* 2004; 20: 179–82.

Effects on the eyes. Studies in *animals* have suggested that some statins could cause cataracts, but this has not been confirmed in humans. Although a study[1] with lovastatin found lens opacities in 13 of 101 patients after treatment for 18 weeks, no deterioration in visual function was found in 11 of these who continued lovastatin and were followed up for an average of 26 months from the start of treatment. Similarly, no differences were found in the development of lens opacities or in changes in visual acuity between patients treated with lovastatin for 48 weeks and patients taking placebo in a study of 8245 patients.[2] A large case-control study[3] found no evidence that use of therapeutic statin doses was associated with the development of cataracts, although the risk did appear to be increased in patients taking simvastatin with erythromycin. Further observational studies have suggested that statins may have beneficial effects; in one study[4] there was no effect on the overall incidence of cataract but the risk of developing nuclear cataract appeared to be decreased, while another study[5] reported a reduction in the overall incidence but this was not significant for any specific cataract type.

For mention of ocular haemorrhage in patients taking statins, see Effects on the Blood, above.

1. Hunninghake DB, *et al.* Lovastatin: follow-up ophthalmologic data. *JAMA* 1988; 259: 354–5.
2. Laties AM, *et al.* The human lens after 48 weeks of treatment with lovastatin. *N Engl J Med* 1990; 323: 683–4.
3. Schlienger RG, *et al.* Risk of cataract in patients treated with statins. *Arch Intern Med* 2001; 161: 2021–6.
4. Klein BEK, *et al.* Statin use and incident nuclear cataract. *JAMA* 2006; 295: 2752–8.
5. Tan JSL, *et al.* Statin use and the long-term risk of incident cataract: the Blue Mountains Eye Study. *Am J Ophthalmol* 2007; 143: 687–9.

Effects on the hair. Between its introduction in Australia and 1993, 16 cases of alopecia associated with the use of simvastatin had been reported to the Adverse Drug Reactions Advisory Committee.[1] Most cases involved either excessive hair loss or hair thinning, although 2 cases of hair loss in patches and 1 resembling alopecia areata were reported. Onset occurred between 3 days and 15 months after starting therapy. Progressive hair loss has also been reported[2] in a woman within 6 weeks of starting atorvastatin; the hair regrew when atorvastatin was stopped but alopecia recurred when therapy was restarted 5 months later.

1. Anonymous. Simvastatin and alopecia. *Aust Adverse Drug React Bull* 1993; 12: 7.
2. Segal AS. Alopecia associated with atorvastatin. *Am J Med* 2002; 113: 171.

Effects on the kidneys. *Proteinuria* was reported in 10 patients taking simvastatin 40 mg daily.[1] The protein loss was of a pattern typical for increased glomerular permeability. In 2 patients proteinuria disappeared when simvastatin was withdrawn and recurred on its subsequent reintroduction. Proteinuria has also been seen with rosuvastatin, and was found to be dose-dependent.[2] However, there is also some evidence that statins may improve proteinuria (see Kidney Disorders under Uses, p. 1491.3).

Acute tubulointerstitial *nephritis* developed[3] in a patient receiving high-dose therapy with rosuvastatin. It resolved over 3 weeks when rosuvastatin was stopped, but recurred 2 weeks after rechallenge. A similar reaction was noted with atorvastatin, but improved with dose reduction, and the patient was finally stabilised on simvastatin without a further recurrence.

Renal failure due to rhabdomyolysis has been reported rarely (see under Effects on Skeletal Muscle, p. 1493.2).

1. Deslypere JP, *et al.* Proteinuria as complication of simvastatin treatment. *Lancet* 1990; 336: 1453.
2. Agarwal R. Effects of statins on renal function. *Am J Cardiol* 2006; 97: 748–55.
3. van Zyl-Smit R, *et al.* Renal tubular toxicity of HMG-CoA reductase inhibitors. *Nephrol Dial Transplant* 2004; 19: 3176–9.

Effects on the liver. Statins cause dose-related increases in liver enzymes but the incidence appears to be low with low to moderate doses[1] and serious hepatic effects appear to be rare.[2] Although monitoring of liver function tests is advised, the value of routine assessment has been questioned.[3] There is some evidence[4] that the incidence of hepatic reactions may be higher with fluvastatin than with other statins, but this is not yet established.

There have also been case reports[5–8] of cholestasis and acute hepatitis in patients receiving statins.

1. de Denus S, *et al.* Statins and liver toxicity: a meta-analysis. *Pharmacotherapy* 2004; 24: 584–91.
2. Charles ED, *et al.* Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am J Med* 2005; 118: 618–24.
3. Kostner K, Howes LG. Statins and monitoring of liver function tests. *Drug Safety* 2007; 30: 1–4.
4. Conforti A, *et al.* Fluvastatin and hepatic reactions: a signal from spontaneous reporting in Italy. *Drug Safety* 2006; 29: 1163–72.
5. Jiménez-Alonso J, *et al.* Atorvastatin-induced cholestatic hepatitis in a young woman with systemic lupus erythematosus. *Arch Intern Med* 1999; 159: 1811–12.
6. Wierzbicki AS, Crook MA. Cholestatic liver dysfunction. *Lancet* 1999; 354: 954.
7. Batey RG, Harvey M. Cholestasis associated with the use of pravastatin sodium. *Med J Aust* 2002; 176: 561.
8. Rahier JF, *et al.* Severe acute cholestatic hepatitis with prolonged cholestasis and bile-duct injury following atorvastatin therapy: a case report. *Acta Gastroenterol Belg* 2008; 71: 318–20.

Effects on the lungs. Interstitial lung disorders, including hypersensitivity pneumonitis, have been reported with several statins.[1–5] In some cases the condition improved when the statin was stopped[2] but treatment with corticosteroids and immunosuppressants was required in some patients[1–4] and progressive disease and fatalities have occurred.[4]

1. de Groot REB, *et al.* Interstitial lung disease with pleural effusion caused by simvastin [sic]. *J Intern Med* 1996; 239: 361–3.
2. Liebhaber ML *et al.* Polymyalgia, hypersensitivity pneumonitis and other reactions in patients receiving HMG-CoA reductase inhibitors: a report of ten cases. *Chest* 1999; 115: 886–9.

3. Lantuejoul S, *et al.* Statin-induced fibrotic nonspecific interstitial pneumonia. *Eur Respir J* 2002; 19: 577–80.
4. Walker T, *et al.* Potential link between HMG-CoA reductase inhibitor (statin) use and interstitial lung disease. *Med J Aust* 2007; 186: 91–4.
5. Fernández AB, *et al.* Statins and interstitial lung disease: a systematic review of the literature and of Food and Drug Administration adverse event reports. *Chest* 2008; 134: 824–30.

Effects on mental function. There have been conflicting reports of the effects of statins on mental function, and adverse psychiatric reactions have been reported with statins and with other lipid regulating drugs, although the exact association is unclear.

There have been a few case reports of *depressive symptoms* developing in patients treated with pravastatin[1] or simvastatin.[2] The symptoms appeared during the first few weeks or months of treatment. However, randomised studies investigating the effects of lowering cholesterol on mental function have found no effect on mood disorders (with simvastatin[3]) or psychological well-being (with lovastatin[4] or pravastatin[5]), and epidemiological studies have suggested that use of statins may be associated with improved psychological status[6] and a reduction in the risk of depression and suicide.[7]

Impairment of cognitive function has been reported with statins. In the study using lovastatin,[4] reductions in some measures of cognitive function were noted, and similar results were found in a study using simvastatin.[8] New onset cognitive impairment in a patient a week after starting simvastatin resolved when the drug was stopped but recurred on rechallenge with a lower dose,[9] while analyses of reports to adverse drug reaction reporting databases[10,11] have found several cases of memory loss in patients receiving statins, some of which were confirmed by rechallenge. However, clinical studies have not found statins to have an adverse effect on cognition, and there is epidemiological evidence that use of statins may reduce the incidence of dementia (see under Uses, p. 1491.2). A study with atorvastatin[12] also found beneficial effects on cognitive function.

Other psychiatric effects that have been noted in reports to another adverse drug reaction reporting database[13] include 5 cases of aggressive reactions, all of which resolved when the statin was stopped.

See also Effects on Sleep Patterns, below.

1. Lechleitner M, *et al.* Depressive symptoms in hypercholesterolaemic patients treated with pravastatin. *Lancet* 1992; 340: 910.
2. Duits N, Bos FM. Depressive symptoms and cholesterol-lowering drugs. *Lancet* 1993; 341: 114.
3. Wardle J, *et al.* Randomised placebo controlled trial of effect on mood of lowering cholesterol concentration. *BMJ* 1996; 313: 75–8.
4. Muldoon MF, *et al.* Effects of lovastatin on cognitive function and psychological well-being. *Am J Med* 2000; 108: 538–47.
5. Stewart RA, *et al.* Long-term assessment of psychological well-being in a randomized placebo-controlled trial of cholesterol reduction with pravastatin. *Arch Intern Med* 2000; 160: 3144–52.
6. Young-Xu Y, *et al.* Long-term statin use and psychological well-being. *J Am Coll Cardiol* 2003; 42: 690–7.
7. Yang C-C, *et al.* Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med* 2003; 163: 1926–32.
8. Muldoon MF, *et al.* Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *Am J Med* 2004; 117: 823–9.
9. Padala KP, *et al.* Simvastatin-induced decline in cognition. *Ann Pharmacother* 2006; 40: 1880–3.
10. Wagstaff LR, *et al.* Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003; 23: 871–80.
11. Health Canada. Statins and memory loss. *Can Adverse React News* 2005; 15 (4): 2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcel_v15n4-eng.pdf (accessed 19/08/08)
12. Parale GP, *et al.* Effects of atorvastatin on higher functions. *Eur J Clin Pharmacol* 2006; 62: 259–65.
13. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Safety* 2007; 30: 195–201.

Effects on the nervous system. Treatment with statins may be associated with the development of peripheral neuropathy,[1] although the reaction appears to be rare. Up to 2005, the Australian Adverse Drug Reactions Advisory Committee had received 281 reports[2] of both sensory and sensorimotor peripheral neuropathies associated with statins. Time to onset of symptoms ranged from after the first dose to 4.5 years. Recovery was seen on withdrawal in about half of the cases, including in some diabetics, and there were some reports of positive rechallenge. In 21 cases symptoms persisted at the time of reporting, up to 8 months after the statin was stopped, and in a further 2 reports the symptoms were unresolved after 3 and 5 years respectively. Similar patterns have been noted elsewhere.[3] A case-control study[4] found that the risk of neuropathy was substantially increased in users of statins although the number of cases was small, and the authors concluded that the benefits of therapy generally outweighed the risks.

Reports[5] of upper motor neurone lesions similar to amyotrophic lateral sclerosis (ALS) in patients taking statins prompted the FDA to analyse data from their spontaneous adverse event reporting system; however, the incidence of ALS with statins and placebo was similar.[6]

1. Backes JM, Howard PA. Association of HMG-CoA reductase inhibitors with neuropathy. *Ann Pharmacother* 2003; 37: 274–8.
2. Adverse Drug Reactions Advisory Committee (ADRAC). Statins and peripheral neuropathy. *Aust Adverse Drug React Bull* 2005; 24: 6. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0504.pdf (accessed 30/05/08)
3. de Langen JJ, van Puijenbroek EP. HMG-CoA-reductase inhibitors and neuropathy: reports to the Netherlands Pharmacovigilance Centre. *Neth J Med* 2006; 64: 334–8.
4. Gaist D, *et al.* Statins and risk of polyneuropathy: a case-control study. *Neurology* 2002; 58: 1333–7.
5. Edwards IR, *et al.* Statins, neuromuscular degenerative disease and an amyotrophic lateral sclerosis-like syndrome: an analysis of individual case safety reports from Vigibase. *Drug Safety* 2007; 30: 515–25.
6. Colman E, *et al.* An evaluation of a data mining signal for amyotrophic lateral sclerosis and statins detected in FDA's spontaneous adverse event reporting system. *Pharmacoepidemiol Drug Safety* 2008; 17: 1068–76.

Effects on the pancreas. Statins may cause pancreatitis but the incidence appears to be low,[1,2] and a case-control study[3] failed to support a strong association.

1. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. *Drug Safety* 2006; 29: 1123–32.
2. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. *Pharmacotherapy* 2006; 26: 414–22.
3. Thisted H, *et al.* Statins and the risk of acute pancreatitis: a population-based case-control study. *Aliment Pharmacol Ther* 2006; 23: 185–90.

Effects on sexual function. There have been reports of *erectile dysfunction* in some men receiving statins. Five men receiving simvastatin developed impotence,[1] which resolved when fluvastatin was substituted in 4 of them. In another case,[2] impotence occurred in a patient receiving lovastatin, and recurred when therapy was changed to pravastatin. Up to 1995, the Australian Adverse Drug Reactions Advisory Committee[3] had received 28 reports of impotence associated with simvastatin, which had recurred on rechallenge in 4 cases. A report[4] from the French and Spanish drug monitoring systems, and an observational study[5] in high-risk cardiovascular patients, supported the association between statins and erectile dysfunction, and a systematic review[6] came to similar conclusions. However, it has been pointed out[7] that the increased risk of sexual dysfunction with statins in the Scandinavian Simvastatin Survival Study was not statistically significant, and there has also been a small study[8] suggesting that atorvastatin may improve erectile function in men with hyperlipidaemia as the only risk factor.

Decreased libido has also been reported with statins. Serum-testosterone concentrations were measured in 2 of 8 patients reported to the Netherlands Pharmacovigilance Centre and were found to be low;[9] they rose after the statin was stopped.

Testicular pain has been reported[10] in a 54-year-old patient 7 months after starting lovastatin. The pain resolved when lovastatin was stopped, but recurred with both simvastatin and atorvastatin. The mechanism for the reaction was unclear.

There has also been a report[11] of a *low sperm count* in a patient receiving lovastatin.

Gynaecomastia occurred in a patient 6 months after changing from simvastatin to atorvastatin.[12] Symptoms improved when atorvastatin was stopped and did not recur when treatment with simvastatin was restarted.

1. Jackson G. Simvastatin and impotence. *BMJ* 1997; 315: 31.
2. Halkin A, *et al.* HMG-CoA reductase inhibitor-induced impotence. *Ann Pharmacother* 1996; 30: 192.
3. Australian Adverse Drug Reactions Advisory Committee (ADRAC). Simvastatin and adverse endocrine effects in men. *Aust Adverse Drug React Bull* 1995; 14: 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9508.htm (accessed 30/05/08)
4. Carvajal A, *et al.* HMG CoA reductase inhibitors and impotence: two case series from the Spanish and French drug monitoring systems. *Drug Safety* 2006; 29: 143–9.
5. Solomon H, *et al.* Erectile dysfunction and statin treatment in high cardiovascular risk patients. *Int J Clin Pract* 2006; 60: 141–5.
6. Rizvi K, *et al.* Do lipid-lowering drugs cause erectile dysfunction? A systematic review. *Fam Pract* 2002; 19: 95–8.
7. Pedersen TR, Færgeman O. Simvastatin seems unlikely to cause impotence. *BMJ* 1999; 318: 192.
8. Saltzman EA, *et al.* Improvement in erectile function in men with organic erectile dysfunction by correction of elevated cholesterol levels: a clinical observation. *J Urol (Baltimore)* 2004; 172: 255–8.
9. de Graaf L, *et al.* Is decreased libido associated with the use of HMG-CoA-reductase inhibitors? *Br J Clin Pharmacol* 2004; 58: 326–8.
10. Linnebur AS, Hiatt WH. Probable statin-induced testicular pain. *Ann Pharmacother* 2007; 41: 138–42.
11. Hildebrand RD, Hepperlen TW. Lovastatin and hypospermia. *Ann Intern Med* 1990; 112: 549–50.
12. Hammons KB, *et al.* Golf-inhibiting gynecomastia associated with atorvastatin therapy. *Pharmacotherapy* 2006; 26: 1165–8.

Effects on skeletal muscle. The association between muscle disorders and statins is well known.[1-9] Mild *myalgia* is relatively common, but *myositis* and *myopathy*, with elevation of creatine kinase, may also occur. *Rhabdomyolysis*,[10,11] which involves severe muscle damage, substantial elevation of creatine kinase and myoglobinuria leading to renal impairment, occurs more rarely, but has resulted in fatalities. Muscle toxicity is dose-related and the risk appears to be broadly similar with all of the currently-marketed statins;[5,6,12] the incidence with cerivastatin was found to be considerably higher and this led to its withdrawal worldwide in 2001. Patients with complex medical problems, including renal impairment and possibly endocrine disorders such as hypothyroidism, may be at increased risk of muscle toxicity; drug interactions may also contribute (see p. 1494.2). Myopathy has been reported with other lipid regulating drugs, particularly fibrates, and the risk may be increased in patients with severe hyperlipidaemia who require combination therapy; careful monitoring is required if statins and fibrates are used together.[6,13] The UK CSM[1] and a joint committee of the American College of Cardiology, American Heart Association, and National Heart, Lung and Blood Institute,[6] have both advised that patients treated with statins should consult their doctor if they develop muscle pain, tenderness, or weakness and that treatment should be stopped if muscle toxicity occurs or is suspected clinically or if creatine phosphokinase is markedly raised or progressively rising. If continued therapy is required, the dose may be reduced or another statin or alternative lipid regulating drug may be tried, although the risk of recurrent muscle problems appears quite high.[11] An algorithm for diagnosis and management of statin-associated myalgia has been suggested.[14]

The mechanism by which statins cause muscle toxicity is not clear, but it has been suggested that depletion of ubidecarenone concentrations may be involved.[15] Although positive results have been reported with ubidecarenone supplementation[16] evidence of benefit is limited and it is not generally recommended.[17]

Other muscular disorders that have been reported in patients receiving statins include *dermatomyositis* and *polymyositis*,[18] and *myasthenia gravis*.[19-21]

1. CSM/MCA. HMG CoA reductase inhibitors (statins) and myopathy. *Current Problems* 2002; 28: 8–9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0074526&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
2. Adverse Drug Reactions Advisory Committee (ADRAC). Fluvastatin and muscle disorders—a class effect. *Aust Adverse Drug React Bull* 1997; 16: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 30/05/08)
3. Ucar M, *et al.* HMG-CoA reductase inhibitors and myotoxicity. *Drug Safety* 2000; 22: 441–57.
4. Omar MA, *et al.* Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother* 2001; 35: 1096–1107.
5. Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. *Ann Pharmacother* 2002; 36: 288–95.
6. Pasternak RC, *et al.* ACC/AHA/NHLBI Clinical Advisory on the use and safety of statins. *Circulation* 2002; 106: 1024–8. Also available at: http://circ.ahajournals.org/cgi/reprint/106/8/1024.pdf (accessed 30/05/08)
7. Adverse Drug Reactions Advisory Committee (ADRAC). Risk factors for myopathy and rhabdomyolysis with the statins. *Aust Adverse Drug React Bull* 2004; 23: 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0402.pdf (accessed 30/05/08)
8. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004; 116: 408–16.
9. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med* 2009; 150: 858–68.
10. Graham DJ, *et al.* Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; 292: 2585–90.
11. Antons KA, *et al.* Clinical perspectives of statin-induced rhabdomyolysis. *Am J Med* 2006; 119: 400–9.
12. Staffa JA, *et al.* Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med* 2002; 346: 539–540.
13. Shek A, Ferrill MJ. Statin-fibrate combination therapy. *Ann Pharmacother* 2001; 35: 908–917.
14. Jacobson TA. Toward "pain-free" statin prescribing: clinical algorithm for diagnosis and management of myalgia. *Mayo Clin Proc* 2008; 83: 687–700.
15. Hargreaves IP, *et al.* The effect of HMG-CoA reductase inhibitors on coenzyme Q_{10}: possible biochemical/clinical implications. *Drug Safety* 2005; 28: 659–76.
16. Wallravens PA, *et al.* Lovastatin, isoprenes, and myopathy. *Lancet* 1989; ii: 1097–8.
17. Levy HB, Kohlhaas HK. Considerations for supplementing with coenzyme Q_{10} during statin therapy. *Ann Pharmacother* 2006; 40: 290–4.
18. Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007; 21: 17–24.
19. Parmar B, *et al.* Statins, fibrates, and ocular myasthenia. *Lancet* 2002; 360: 717.
20. Cartwright MS, *et al.* Statin-associated exacerbation of myasthenia gravis. *Neurology* 2004; 63: 2188.
21. Purvin V, *et al.* Statin-associated myasthenia gravis: report of 4 cases and review of the literature. *Medicine (Baltimore)* 2006; 85: 82–5.

Effects on sleep patterns. Changes to sleep patterns have been reported with lipophilic statins such as lovastatin[1-3] and simvastatin,[4] but appear to be less common with pravastatin,[1] possibly because it is hydrophilic and less likely to cross the blood-brain barrier. However, a large placebo-controlled study[5] found that simvastatin had no effect on sleep patterns, and smaller studies that assessed sleep using questionnaires[6] or polysomnography[7-9] found no significant effects with any of the statins, although some patients appeared to have underlying sleep disorders.

Nightmares and sleep disturbances in a patient taking simvastatin and metoprolol resolved when treatment was changed to pravastatin and atenolol.[10] There has been a report of nightmares with atorvastatin, which resolved when the drug was stopped but recurred on rechallenge.[11]

1. Schaefer EJ. HMG-CoA reductase inhibitors for hypercholesterolemia. *N Engl J Med* 1988; 319: 1222.
2. Rosenson RS, Goranson NL. Lovastatin-associated sleep and mood disturbances. *Am J Med* 1993; 95: 548–9.
3. Sinzinger H, *et al.* Sleep disturbance and appetite loss after lovastatin. *Lancet* 1994; 343: 973.

4. Barth JD, *et al.* Inhibitors of hydroxymethylglutaryl coenzyme A reductase for treating hypercholesterolaemia. *BMJ* 1990; 301: 669.
5. Keech AC, *et al.* Absence of effects of prolonged simvastatin therapy on nocturnal sleep in a large randomized placebo-controlled study. *Br J Clin Pharmacol* 1996; 42: 483–90.
6. Black DM, *et al.* Sleep disturbances and HMG CoA reductase inhibitors. *JAMA* 1990; 264: 1105.
7. Eckernäs S-Å, *et al.* The effects of simvastatin and pravastatin on objective and subjective measures of nocturnal sleep: a comparison of two structurally different HMG CoA reductase inhibitors in patients with primary moderate hypercholesterolaemia. *Br J Clin Pharmacol* 1993; 35: 284–9.
8. Kostis JB, *et al.* Central nervous system effects of HMG CoA reductase inhibitors: lovastatin and pravastatin on sleep and cognitive performance in patients with hypercholesterolemia. *J Clin Pharmacol* 1994; 34: 989–96.
9. Ehrenberg BL, *et al.* Comparison of the effects of pravastatin and lovastatin on sleep disturbance in hypercholesterolemic subjects. *Sleep* 1999; 22: 117–21.
10. Boriani G, *et al.* Nightmares and sleep disturbances with simvastatin and metoprolol. *Ann Pharmacother* 2001; 35: 1292.
11. Gregoor PJHS. Atorvastatin may cause nightmares. *BMJ* 2006; 332: 950.

Precautions

Statins should not be given to patients with active liver disease (but see also Hepatic Impairment, below). Liver function should be assessed before starting treatment and subsequently when clinically indicated; additional assessment after 3 months and before and after dosage increases has been advised for some statins, particularly when high doses are given. Statins should not be used in patients who already have unexplained persistently raised serum-aminotransferase concentrations and should be stopped if marked or persistent increases in serum-aminotransferase concentrations occur. They should be avoided during pregnancy since there is a possibility that they could interfere with fetal sterol synthesis; there have been reports of congenital abnormalities associated with statins (see Pregnancy, below).

All statins may cause myopathy and rhabdomyolysis, especially at higher doses. High doses of statins should therefore be limited to those patients with severe hypercholesterolaemia and high cardiovascular risk, who do not achieve their target cholesterol concentration at lower doses, provided benefits outweigh the potential risk. They should be used with caution in patients at risk of rhabdomyolysis, and particularly in patients taking drugs that increase plasma concentrations of the statin (see Interactions, below); the statin should be stopped if creatine phosphokinase increases significantly or if myopathy is diagnosed.

Statins should be used with caution in patients with renal impairment as the risk of myopathy is increased. Dose reduction may be required for statins that are excreted by the kidney and for those with a particularly high risk of myopathy (see Administration in Renal Impairment under Uses of the individual drugs for further details).

Children. For discussion of concerns relating to the use of statins in children, see Administration in Children under Uses, p. 1490.2.

Hepatic impairment. Although licensed product information contra-indicates the use of statins in patients with active liver disease, there is some interest in the possibility of using them in selected patients with chronic liver disease such as non-alcoholic fatty liver disease or non-alcoholic steatohepatitis.[1-3] The Liver Expert Panel of the National Lipid Association in the USA assessed the safety of statins, and concluded that although they should remain contra-indicated in patients with decompensated cirrhosis or acute liver failure (in whom, given the gravity of their illness, they were unlikely to be a relevant option in any case), there was no reason to do so in patients with chronic liver disease or compensated cirrhosis.[1]

A subsequent comment by UK experts[2] noted that use in patients with chronic liver disease and elevated transaminase values remained contentious. Those with AST and ALT concentrations less than 3 times above the normal upper limit could be offered statin therapy but at the lowest possible dose, and liver enzymes should be reassessed within 4 weeks; if no major change occurred, treatment could continue and values be monitored every 6 weeks for the next 3 months, and every 3 months thereafter. If values doubled from their original readings, treatment should be stopped, although rechallenge was possible once they returned to normal baseline values. They recommended that treatment should not be given to the following groups:

- those with transaminase values more than 3 times above the normal upper limit (although this was an arbitrary limit rather than an evidence-based one)
- those with evidence of impaired liver synthesis, e.g. low serum albumin or increased prothrombin time
- those with acute hepatitis of any cause
- those with Child B or C cirrhosis

It was noted that patients with end-stage liver disease often have low total cholesterol due to poor hepatic synthesis, and as such rarely require statin therapy.[2]

1. Cohen DE, *et al.* National Lipid Association Statin Safety Task Force Liver Expert Panel. An assessment of statin safety by hepatologists. *Am J Cardiol* 2006; 97: 77C–81C.
2. Cash J, *et al.* Statin safety and chronic liver disease. *Int J Clin Pract* 2008; 62: 1831–5.
3. Tandra S, Vuppalanchi R. Use of statins in patients with liver disease. *Curr Treat Options Cardiovasc Med* 2009; 11: 272–8.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies simvastatin as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. Statins are generally contra-indicated in pregnancy since there is a possibility that they might affect fetal sterol synthesis whereas the risk to the mother from stopping treatment temporarily is usually very low. Evidence that statins have adverse effects on the fetus, however, is limited. Studies based on postmarketing surveillance[1,2] or pregnancy registry data[3] have generally found that the frequency and range of congenital anomalies reported was similar to that expected in the general population. However, reviews of case reports[4,5] found that the incidence of CNS defects and limb anomalies was higher than expected, suggesting a possible adverse effect of statin exposure; 1 of the 5 cases reported as a CNS defect was later found to have cardiac anomalies only.[6]

1. Manson JM, *et al.* Postmarketing surveillance of lovastatin and simvastatin exposure during pregnancy. *Reprod Toxicol* 1996; 10: 439–46.
2. Pollack PS, *et al.* Pregnancy outcomes after maternal exposure to simvastatin and lovastatin. *Birth Defects Res A Clin Mol Teratol* 2005; 73: 888–96.
3. Ofori B, *et al.* Risk of congenital anomalies in pregnant users of statin drugs. *Br J Clin Pharmacol* 2007; 64: 496–509.
4. Edison RJ, Muenke M. Central nervous system and limb anomalies in case reports of first-trimester statin exposure. *N Engl J Med* 2004; 350: 1579–82.
5. Edison RJ, Muenke M. Mechanistic and epidemiologic considerations in the evaluation of adverse birth outcomes following gestational exposure to statins. *Am J Med Genet* 2004; 131A: 287–98.
6. Edison RJ, Muenke M. Gestational exposure to lovastatin followed by cardiac malformation misclassified as holoprosencephaly. *N Engl J Med* 2005; 352: 2759.

Interactions

The most serious consequence of drug interactions with simvastatin and other statins is the development of myopathy or rhabdomyolysis. Drugs that can cause myopathy when given alone increase the risk of myopathy with all statins; these drugs include fibric acid derivatives (fibrates or gemfibrozil), and nicotinic acid. The risk of myopathy is also increased by drugs that increase the plasma concentrations of statins, by inhibiting their metabolism or by inhibiting their uptake into the liver. Since the statins have different metabolic pathways, these interactions depend on the individual drug concerned. Simvastatin is metabolised by the cytochrome P450 isoenzyme CYP3A4, as are atorvastatin and lovastatin, and interactions may occur with drugs that inhibit this enzyme, including ciclosporin, fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole, erythromycin, clarithromycin, telithromycin, HIV-protease inhibitors, nefazodone, danazol, amiodarone, amlodipine, diltiazem, ranolazine, and verapamil; there may also be a similar interaction with grapefruit juice. Such combinations should be used with caution, if at all, and dose reduction may be advised (see Uses and Administration, p. 1489.3); UK licensed product information contra-indicates the use of simvastatin in patients receiving potent CYP3A4 inhibitors. Fluvastatin is metabolised mainly by CYP2C9 and pitavastatin by glucuronidation, while pravastatin and rosuvastatin are not significantly metabolised; interactions specific to these statins are discussed on p. 1385.2, p. 1471.2, p. 1473.2, and p. 1488.3, respectively.

Statins may also have effects on other drugs. Bleeding and increases in prothrombin time have been reported in patients taking simvastatin or other statins with coumarin anticoagulants.

General reviews.

1. Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; 41: 343–70.
2. Martin J, Krum H. Cytochrome P450 drug interactions within the HMG-CoA reductase inhibitor class: are they clinically relevant? *Drug Safety* 2003; 26: 13–21.
3. CSM/MHRA. Statins and cytochrome P450 interactions. *Current Problems* 2004; 30: 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 30/05/08)
4. Ruiz Bravo AE, *et al.* Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. *Drug Safety* 2005; 28: 263–75.
5. Bottorff MB. Statin safety and drug interactions: clinical implications. *Am J Cardiol* 2006; 97 (suppl 8A): 27C–31C.
6. Neuvonen PJ, *et al.* Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. *Clin Pharmacol Ther* 2006; 80: 565–81.
7. Prisham WH, Horn J. Statin-drug interactions: not a class effect. *Cardiol Rev* 2008; 16: 205–12.

Antiarrhythmics. *Amiodarone* is an inhibitor of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations of statins metabolised by this enzyme, increasing the risk of toxicity. There have been reports[1-3] of myopathy and rhabdomyolysis in patients taking amiodarone and simvastatin (in some cases with other CYP3A4 inhibitors), and a pharmacokinetic study[4] found that amiodarone increased plasma-simvastatin concentrations in healthy subjects. High doses of simvastatin are not recommended in patients taking amiodarone (see Uses and Administration, p. 1489.3).

An asymptomatic increase in serum aminotransferases in a patient receiving rosuvastatin and amiodarone may have been the result of an interaction between the drugs.[5]

1. Roten L, *et al.* Rhabdomyolysis in association with simvastatin and amiodarone. *Ann Pharmacother* 2004; 38: 978–81.
2. Chouhan UM, *et al.* Simvastatin interaction with clarithromycin and amiodarone causing myositis. *Ann Pharmacother* 2005; 39: 1760–1.
3. Ricaurte B, *et al.* Simvastatin–amiodarone interaction resulting in rhabdomyolysis, azotemia, and possible hepatotoxicity. *Ann Pharmacother* 2006; 40: 753–7.
4. Becquemont L, *et al.* Amiodarone interacts with simvastatin but not with pravastatin disposition kinetics. *Clin Pharmacol Ther* 2007; 81: 679–84.
5. Merz T, Fuller SH. Elevated serum transaminase levels resulting from concomitant use of rosuvastatin and amiodarone. *Am J Health-Syst Pharm* 2007; 64: 1818–21.

Antibacterials. *Erythromycin* and other *macrolides* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Increased plasma concentrations of simvastatin have been reported with erythromycin,[1] and increased plasma concentrations of atorvastatin have been found with erythromycin[2] and *clarithromycin*,[3] but not with *azithromycin*.[3] There have been reports of myopathy or rhabdomyolysis in patients receiving simvastatin with clarithromycin,[4] and in patients receiving lovastatin with azithromycin,[5] clarithromycin,[5] or erythromycin.[6]

Rifampicin, an inducer of CYP2C9 and CYP3A4, may reduce the bioavailability of fluvastatin, and has also been reported to reduce the plasma concentration of simvastatin[7] and atorvastatin.[8]

There have been reports of rhabdomyolysis in patients receiving atorvastatin[9] or simvastatin[10] with *fusidic acid*.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; 64: 177–82.
2. Siedlik PH, *et al.* Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol* 1999; 39: 501–4.
3. Amsden GW, *et al.* A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol* 2002; 42: 444–9.
4. Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001; 35: 26–31.
5. Grunden JW, Fisher KA. Lovastatin-induced rhabdomyolysis possibly associated with clarithromycin and azithromycin. *Ann Pharmacother* 1997; 31: 859–63.
6. Ayanian JZ, *et al.* Lovastatin and rhabdomyolysis. *Ann Intern Med* 1988; 109: 682–3.
7. Kyrklund C, *et al.* Rifampin greatly reduces plasma simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 2000; 68: 592–7.
8. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; 78: 154–67.
9. Wenisch C, *et al.* Acute rhabdomyolysis after atorvastatin and fusidic acid therapy. *Am J Med* 2000; 109: 78.
10. Yuen SLS, McGarity B. Rhabdomyolysis secondary to interaction of fusidic acid and simvastatin. *Med J Aust* 2003; 179: 172.

Anticoagulants. For reports of bleeding and increased prothrombin time in patients receiving oral anticoagulants with statins, see Lipid Regulating Drugs, p. 1534.3.

Antidepressants. Myositis and rhabdomyolysis, with raised liver enzyme values, have been reported[1-4] in patients given simvastatin with *nefazodone*; in one case[3] the reaction appeared to be precipitated by the addition of azithromycin. Increased creatine kinase concentrations also occurred in a patient given pravastatin with nefazodone.[5]

A study[6] in healthy subjects found that *St John's wort* reduced the plasma concentration of simvastatin but had no effect on pravastatin.

1. Jacobson RH, *et al.* Myositis and rhabdomyolysis associated with concurrent use of simvastatin and nefazodone. *JAMA* 1997; 277: 296.
2. Thompson M, Samuels S. Rhabdomyolysis with simvastatin and nefazodone. *Am J Psychiatry* 2002; 159: 1607.
3. Skrabal MZ, *et al.* Two cases of rhabdomyolysis associated with high-dose simvastatin. *Am J Health-Syst Pharm* 2003; 60: 578–81.
4. Karnik NS, Maldonado JR. Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. *Psychosomatics* 2005; 46: 565–8.
5. Alderman CP. Possible interaction between nefazodone and pravastatin. *Ann Pharmacother* 1999; 33: 871.
6. Sugimoto K-i, *et al.* Different effects of St John's Wort on the pharmacokinetics of simvastatin and pravastatin. *Clin Pharmacol Ther* 2001; 70: 518–24.

Antidiabetics. Rhabdomyolysis and acute renal failure developed about 6 weeks after *sitagliptin* was started in an elderly patient already stabilised on several drugs including simvastatin.[1] The condition resolved when both were stopped and did not recur when lovastatin was started. In this case, the patient already had chronic renal impairment, and it was noted that the dose of sitagliptin was double that recommended for his renal function. In another patient taking lovastatin, rhabdomyolysis developed after about 2 weeks of sitagliptin treatment, and recovery occurred after the statin was stopped.[2] In this case, although the patient was 75 years old, she was reported to have a calculated renal function within normal limits. The possible mechanism of an interaction between sitagliptin and statins is unclear. In a study in healthy young subjects, steady-state sitagliptin achieved after 5 days had no significant effect on the pharmacokinetics of a single dose of simvastatin.[3]

1. Kao DP, *et al.* Renal failure and rhabdomyolysis associated with sitagliptin and simvastatin use. *Diabet Med* 2008; 25: 1229–30.
2. DiGregorio RV, Pasikhova Y. Rhabdomyolysis caused by a potential sitagliptin-lovastatin interaction. *Pharmacotherapy* 2009; 29: 352–6.
3. Bergman AJ, *et al.* Effect of sitagliptin on the pharmacokinetics of simvastatin. *J Clin Pharmacol* 2009; 49: 483–8.

Antifungals. *Itraconazole* and *ketoconazole* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may increase plasma concentrations and the risk of myopathy with some statins. Raised plasma concentrations of simvastatin,[1,2] lovastatin,[3,4] and atorvastatin[5] have been reported with itraconazole, whereas the effect on pravastatin,[1] rosuvastatin,[6] or fluvastatin[4] appears to be minimal. Myopathy and rhabdomyolysis have been reported with simvastatin and itraconazole[2,7] or ketoconazole,[8] and with lovastatin and itraconazole.[9] *Fluconazole* inhibits CYP2C9 and has been reported[10] to increase the plasma concentration of fluvastatin. There has also been a report[11] of rhabdomyolysis in a patient taking fluconazole and simvastatin.

1. Neuvonen PJ, *et al.* Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole. *Clin Pharmacol Ther* 1998; 63: 332–41.
2. Segaert MF, *et al.* Drug-interaction-induced rhabdomyolysis. *Nephrol Dial Transplant* 1996; 11: 1846–7.
3. Neuvonen PJ, Jalava K-M. Itraconazole drastically increases plasma concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1996; 60: 54–61.
4. Kivistö KT, *et al.* Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol* 1998; 46: 49–53.
5. Kantola T, *et al.* Effect of itraconazole on the pharmacokinetics of atorvastatin. *Clin Pharmacol Ther* 1998; 64: 58–65.
6. Cooper KJ, *et al.* Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2003; 73: 322–9.
7. Horn M. Coadministration of itraconazole with hypolipidemic agents may induce rhabdomyolysis in healthy individuals. *Arch Dermatol* 1996; 132: 1254.
8. Gilad R, Lampl Y. Rhabdomyolysis induced by simvastatin and ketoconazole treatment. *Clin Neuropharmacol* 1999; 22: 295–7.
9. Lees RS, Lees AM. Rhabdomyolysis from the coadministration of lovastatin and the antifungal agent itraconazole. *N Engl J Med* 1995; 333: 664–5.
10. Kantola T, *et al.* Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol* 2000; 56: 225–9.
11. Shaukat A, *et al.* Simvastatin–fluconazole causing rhabdomyolysis. *Ann Pharmacother* 2003; 37: 1032–5.

Antineoplastics. For mention of a potential reduction of cytotoxic effect when *rituximab* is given with statins, see p. 855.1.

Antiplatelet drugs. For discussion of a possible interaction between statins and clopidogrel, see p. 1344.3

Antivirals. *HIV-protease inhibitors* are inhibitors of the cytochrome P450 isoenzyme CYP3A4 and may affect the metabolism of simvastatin and other statins. Studies have shown increased plasma concentrations of both simvastatin and atorvastatin with *nelfinavir*,[1] and with *ritonavir-boosted saquinavir*,[2] whereas the plasma concentration of pravastatin was reduced with ritonavir-boosted saquinavir.[2] Rhabdomyolysis has been reported[3] in a patient taking simvastatin when ritonavir was added to her therapy. Although rosuvastatin is not significantly metabolised, increased plasma concentrations have been reported with *ritonavir-boosted lopinavir*.[4,5]

There has also been a report[6] of rhabdomyolysis in a patient receiving atorvastatin with the non-nucleoside reverse transcriptase inhibitor *delavirdine*.

Efavirenz is an inducer of CYP3A4 and a study in healthy subjects[7] found that it could reduce plasma concentrations of atorvastatin and simvastatin; plasma concentrations of pravastatin were also reduced, although it is not metabolised by CYP3A4.

1. Hsyu P-H, *et al.* Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; 45: 3445–50.
2. Fichtenbaum CJ, *et al.* Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; 16: 569–77.
3. Cheng CH, *et al.* Rhabdomyolysis due to probable interaction between simvastatin and ritonavir. *Am J Health-Syst Pharm* 2002; 59: 728–30.
4. van der Lee M, *et al.* Pharmacokinetics and pharmacodynamics of combined use of lopinavir/ritonavir and rosuvastatin in HIV-infected patients. *Antivir Ther* 2007; 12: 1127–32.
5. Kiser JJ, *et al.* Drug/drug interaction between lopinavir/ritonavir and rosuvastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2008; 47: 570–8.
6. Castro JG, Gutierrez L. Rhabdomyolysis with acute renal failure probably related to the interaction of atorvastatin and delavirdine. *Am J Med* 2002; 112: 505.
7. Gerber JG, *et al.* Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; 39: 307–12.

Calcium-channel blockers. Calcium-channel blockers may increase plasma concentrations of some statins, probably by inhibition of the cytochrome P450 isoenzyme CYP3A4. Pharmacokinetic studies have reported increased plasma concentrations of simvastatin with *verapamil*,[1] and with *diltiazem*,[2] and of lovastatin with diltiazem;[3] the small increase with simvastatin and *lacidipine* was not considered clinically relevant.[4]

The interaction between statins and diltiazem has also been reported in patients. A retrospective study[5] found that the cholesterol-lowering effect of simvastatin was greater in patients who were also receiving diltiazem, and there have also been reports[4-8] of rhabdomyolysis, associated with hepatitis in 1 case,[6] in patients receiving simvastatin and diltiazem together. Rhabdomyolysis[8,9] and hepatitis[9] have also been reported in patients receiving atorvastatin with diltiazem.

For reference to increased bioavailability of verapamil with lovastatin see p. 1525.3.

1. Kantola T, *et al.* Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther* 1998; 64: 177–82.
2. Mousa O, *et al.* The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000; 67: 267–74.
3. Azie NE, *et al.* The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther* 1998; 64: 369–77.
4. Ziviani L, *et al.* The effects of lacidipine on the steady/state plasma concentrations of simvastatin in healthy subjects. *Br J Clin Pharmacol* 2001; 51: 147–52.
5. Yeo KR, *et al.* Enhanced cholesterol reduction by simvastatin in diltiazem-treated patients. *Br J Clin Pharmacol* 1999; 48: 610–615.
6. Kanathur N, *et al.* Simvastatin–diltiazem drug interaction resulting in rhabdomyolysis and hepatitis. *Tenn Med* 2001; 94: 339–41.
7. Peces R, Pobes A. Rhabdomyolysis associated with concurrent use of simvastatin and diltiazem. *Nephron* 2001; 89: 117–118.
8. Gladding P, *et al.* Potentially fatal interaction between diltiazem and statins. *Ann Intern Med* 2004; 140: W31. Available at: http://www.annals.org/cgi/reprint/140/8/W-31.pdf (accessed 14/11/07)
9. Lewin JJ, *et al.* Rhabdomyolysis with concurrent atorvastatin and diltiazem. *Ann Pharmacother* 2002; 36: 1546–9.

Colchicine. For reports of additive muscle toxicity with statins and colchicine, see Cardiovascular Drugs under Interactions of Colchicine, p. 606.2.

Danazol. Rhabdomyolysis has been reported[1] in a patient receiving lovastatin with several other drugs; it was considered that an interaction with danazol was the most likely cause. A similar reaction has been reported[2] with simvastatin.

1. Dallaire M, Chamberland M. Rhabdomyolyse sévère chez un patient recevant lovastatine, danazol et doxycycline. *Can Med Assoc J* 1994; 150: 1991–4.
2. Andreou ER, Ledger S. Potential drug interaction between simvastatin and danazol causing rhabdomyolysis. *Can J Clin Pharmacol* 2003; 10: 172–4.

Endothelin receptor antagonists. *Bosentan* is an inducer of the cytochrome P450 isoenzyme CYP3A4 and has been reported[1] to reduce plasma-simvastatin concentrations in healthy subjects.

1. Dingemanse J, *et al.* Investigation of the mutual pharmacokinetic interactions between bosentan, a dual endothelin receptor antagonist, and simvastatin. *Clin Pharmacokinet* 2003; 42: 293–301.

Fruit juices. *Grapefruit juice* inhibits the cytochrome P450 isoenzyme CYP3A4 and studies using concentrated grapefruit juice have reported increased plasma concentrations of simvastatin,[1] lovastatin,[2] and atorvastatin.[3] A study[4] using less concentrated grapefruit juice found only minimal effect on the activity of lovastatin, but the conclusions of this study have been criticised;[5] studies using normal strength grapefruit juice have found considerable increases in plasma concentrations of atorvastatin[6] and simvastatin.[7] There is also a case report[8] of a woman receiving simvastatin who developed symptoms of rhabdomyolysis 4 days after she started eating one grapefruit each day. Statins that are not significantly metabolised by CYP3A4, such as pitavastatin[6] and pravastatin,[3,9] do not appear to be affected.

Rhabdomyolysis has also been reported[10] in a patient taking rosuvastatin and ezetimibe when he started drinking *pomegranate juice* regularly.

1. Lilja JJ, *et al.* Grapefruit juice–simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998; 64: 477–83.
2. Kantola T, *et al.* Grapefruit juice greatly increases serum concentrations of lovastatin and lovastatin acid. *Clin Pharmacol Ther* 1998; 63: 397–402.
3. Lilja JJ, *et al.* Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999; 66: 118–27.
4. Rogers JD, *et al.* Grapefruit juice has minimal effects on plasma concentrations of lovastatin-derived 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Clin Pharmacol Ther* 1999; 66: 358–66.
5. Bailey DG, Dresser GK. Grapefruit juice–lovastatin interaction. *Clin Pharmacol Ther* 2000; 67: 690.
6. Ando H, *et al.* Effects of grapefruit juice on the pharmacokinetics of pitavastatin and atorvastatin. *Br J Clin Pharmacol* 2005; 60: 494–7.
7. Lilja JJ, *et al.* Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. *Br J Clin Pharmacol* 2004; 58: 56–60.
8. Dreier JP, Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. *Neurology* 2004; 62: 670.
9. Fukazawa I, *et al.* Effects of grapefruit juice on pharmacokinetics of atorvastatin and pravastatin in Japanese. *Br J Clin Pharmacol* 2004; 57: 448–55.
10. Sorokin AV, *et al.* Rhabdomyolysis associated with pomegranate juice consumption. *Am J Cardiol* 2006; 98: 705–6.

Immunosuppressants. Myopathy and rhabdomyolysis have been reported in patients receiving atorvastatin,[1] lovastatin,[2-4] or simvastatin[5-7] with immunosuppressant regimens including *ciclosporin*. The mechanism of the interaction may be additive toxicity, since both statins and ciclosporin are known to cause myopathy, but effects on plasma concentrations may also be involved. Pharmacokinetic studies have shown that ciclosporin increases the plasma concentrations of atorvastatin,[8,9] fluvastatin,[10,11] lovastatin,[12] pravastatin,[12,13] rosuvastatin,[14] and simvastatin.[15] For the effects of statins on blood-ciclosporin concentrations, see p. 1958.1.

1. Maltz HC, *et al.* Rhabdomyolysis associated with concomitant use of atorvastatin and cyclosporine. *Ann Pharmacother* 1999; 33: 1176–9.
2. Norman DJ, *et al.* Myolysis and acute renal failure in a heart-transplant recipient receiving lovastatin. *N Engl J Med* 1988; 318: 46–7.
3. East C, *et al.* Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med* 1988; 318: 47–8.
4. Corpier CL, *et al.* Rhabdomyolysis and renal injury with lovastatin use: report of two cases in cardiac transplant recipients. *JAMA* 1988; 260: 239–41.
5. Blaison G, *et al.* Rhabdomyolyse causée par la simvastatine chez un transplanté cardiaque sous ciclosporine. *Rev Med Interne* 1992; 13: 61–3.
6. Meier C, *et al.* Rhabdomyolyse bei mit Simvastatin und Ciclosporin behandelten Patienten: Rolle der aktivität des Cytochrom-P450-Enzymsystems der Leber. *Schweiz Med Wochenschr* 1995; 125: 1342–6.
7. Gumprecht J, *et al.* Simvastatin-induced rhabdomyolysis in a CsA-treated renal transplant recipient. *Med Sci Monit* 2003; 9: CS89–CS91.
8. Åsberg A, *et al.* Bilateral pharmacokinetic interaction between cyclosporine A and atorvastatin in renal transplant recipients. *Am J Transplant* 2001; 1: 382–6.
9. Hermann M, *et al.* Substantially elevated levels of atorvastatin and metabolites in cyclosporine-treated renal transplant recipients. *Clin Pharmacol Ther* 2004; 76: 388–91.
10. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996; 62: 1559–64.
11. Park J-W, *et al.* Pharmacokinetics and pharmacodynamics of fluvastatin in heart transplant recipients taking cyclosporine A. *J Cardiovasc Pharmacol Ther* 2001; 6: 351–61.
12. Olbricht C, *et al.* Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997; 62: 311–21.
13. Regazzi MB, *et al.* Altered disposition of pravastatin following concomitant drug therapy with cyclosporin A in transplant recipients. *Transplant Proc* 1993; 25: 2732–4.
14. Simonson SG, *et al.* Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin Pharmacol Ther* 2004; 76: 167–77.
15. Arnadottir M, *et al.* Plasma concentration profiles of simvastatin 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without ciclosporin. *Nephron* 1993; 65: 410–13.

Levothyroxine. For reference to the effect of lovastatin and simvastatin in patients receiving levothyroxine, see Lipid Regulating Drugs, p. 2342.1.

Lipid regulating drugs. Myopathy and myositis are recognised adverse effects of both statins and fibric acid derivatives, including *fibrates* and *gemfibrozil*, and the risk is increased if they are given together. There has also been a report[1] of both hepatotoxicity and rhabdomyolysis in a patient given a statin and gemfibrozil together. The interaction between gemfibrozil and statins may also have a pharmacokinetic basis; studies have shown increased plasma concentrations of atorvastatin,[2] lovastatin,[3] pravastatin,[4] rosuvastatin,[5] and simvastatin[6] when given with gemfibrozil.

Myopathy has also been reported[7,8] in patients given statins with *nicotinic acid*, although a study[9] of adverse effects reported to the FDA found no increase in reports for lovastatin given with nicotinic acid compared with either drug alone.

For reports of increased hepatotoxicity when statins were given with *ezetimibe* see Effects on the Liver, p. 1380.1.

1. Akoglu H, *et al.* Combined organ failure with combination antihyperlipidemic treatment: a case of hepatic injury and acute renal failure. *Ann Pharmacother* 2007; 41: 143–7.
2. Backman JT, *et al.* Rifampin markedly decreases and gemfibrozil increases the plasma concentrations of atorvastatin and its metabolites. *Clin Pharmacol Ther* 2005; 78: 154–67.
3. Kyrklund C, *et al.* Plasma concentrations of active lovastatin acid are markedly increased by gemfibrozil but not by bezafibrate. *Clin Pharmacol Ther* 2001; 69: 340–5.
4. Kyrklund C, *et al.* Gemfibrozil increases plasma pravastatin concentrations and reduces pravastatin renal clearance. *Clin Pharmacol Ther* 2003; 73: 538–44.
5. Schneck DW, *et al.* The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther* 2004; 75: 455–63.
6. Backman JT, *et al.* Plasma concentrations of active simvastatin acid are increased by gemfibrozil. *Clin Pharmacol Ther* 2000; 68: 122–9.

7. Reaven P, Witztum JL. Lovastatin, nicotinic acid, and rhabdomyolysis. *Ann Intern Med* 1988; 109: 597–8.
8. Hill MD, Bilbao JM. Case of the month: February 1999—54 year old man with severe muscle weakness. *Brain Pathol* 1999; 9: 607–8.
9. Alsheikh-Ali AA, Karas RH. Safety of lovastatin/extended release niacin compared with lovastatin alone, atorvastatin alone, pravastatin alone, and simvastatin alone (from the United States Food and Drug Administration adverse event reporting system). *Am J Cardiol* 2007; 99: 379–81.

Proton pump inhibitors. There is a report[1] of rhabdomyolysis causing AV block in a patient receiving atorvastatin when *esomeprazole* and clarithromycin were added to her treatment. As symptoms started before the introduction of clarithromycin, it was thought that a possible contributory mechanism for the interaction was a reduction in the first-pass metabolism of atorvastatin due to the inhibition of p-glycoprotein by esomeprazole.

1. Sipe BE, *et al.* Rhabdomyolysis causing AV blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. *Ann Pharmacother* 2003; 37: 808–11.

Ranolazine. A study[1] in healthy subjects showed that ranolazine moderately increased plasma concentrations of simvastatin but it was not thought that the interaction would be clinically significant.

1. Jerling M, *et al.* Studies to investigate the pharmacokinetic interactions between ranolazine and ketoconazole, diltiazem, or simvastatin during combined administration in healthy subjects. *J Clin Pharmacol* 2005; 45: 422–33.

Pharmacokinetics

Simvastatin is absorbed from the gastrointestinal tract and must be hydrolysed to its active β-hydroxyacid form. Other active metabolites have been detected and several inactive metabolites are also formed. Simvastatin is a substrate for the cytochrome P450 isoenzyme CYP3A4 and undergoes extensive first-pass metabolism in the liver, its primary site of action. Less than 5% of the oral dose has been reported to reach the circulation as active metabolites. Both simvastatin and its β-hydroxyacid metabolite are about 95% bound to plasma proteins. Simvastatin is mainly excreted in the faeces via the bile as metabolites. About 10 to 15% is recovered in the urine, mainly in inactive forms. The half-life of the active β-hydroxyacid metabolite is 1.9 hours.

General reviews.

1. Mauro VF. Clinical pharmacokinetics and practical applications of simvastatin. *Clin Pharmacokinet* 1993; 24: 195–202.
2. Desager J-P, Horsmans Y. Clinical pharmacokinetics of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. *Clin Pharmacokinet* 1996; 31: 348–71.
3. Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors: similarities and differences. *Clin Pharmacokinet* 1997; 32: 403–25.
4. Neuvonen PJ, *et al.* Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. *Clin Pharmacokinet* 2008; 47: 463–74.

Genetic variation. The pharmacokinetics of statins are influenced not only by metabolising enzymes but also by their affinity for organ-specific transporter proteins responsible for their uptake and efflux from cells, in particular in the intestine and liver.[1,2] Statins differ not only in their affinity for cytochrome P450 isoenzymes, but also in their affinity for transporter proteins such as organic anion transporting polypeptides (OATPs) and P-glycoprotein (multidrug resistance 1; MDR1). Both metabolising enzymes and transporter proteins may be subject to ethnic and genetic variation, and it has been suggested that this may explain some of the variability in the efficacy and the risk of adverse effects in different populations.

1. Kim RB. 3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and genetic variability (single nucleotide polymorphisms) in a hepatic drug uptake transporter: what's it all about? *Clin Pharmacol Ther* 2004; 75: 381–5.
2. Tirona RG. Ethnic differences in statin disposition. *Clin Pharmacol Ther* 2005; 78: 311–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Coleflux; Colesterminol; Dosavastatin; Gemistatin; Klonastin; Labistatin; Lipimibe†; Lipoblock; Lipomax; Lisac; Nivelipol; Nosterol; Redusterol; Salvaxil; Sevacol; Several; Simvastec; Sistatin; Tanavat; Vasotenal; Zocor; *Austral.*: Invast; Lipex; Ransim; Simvabell†; Simvahexal; Simvar; Zimstat; Zocor; *Austria*: Gerosim; Nyzoc; Simvarcana; Simvastad; Simvatin; Zocord; *Belg.*: Cholemed; Docsimvasta†; Simvafour; Simvastamed†; Zocor; *Braz.*: Androlip; Clinfar; Lipistatina; Lipotex†; Liptrat; Menocol; Mivalen; Revastin; Sinvalip; Sinvane†; Sinvascor; Sinvastacor; Sinvastamed; Sinvaston; Sinvatrox; Sinvax; Vaslip; Vastatil; Zocor; *Canad.*: Zocor; *Chile*: Nimicor; Simvass; Vasomed; Vasotenal†; Zocor; *China*: Bo Zhan Tong (博占同); Jian Zhi Ting (剑之亭); Jie Zhi (捷芝); Ka Di Ke (卡地克); Li Shu Da (理舒达); Lizhishu (利之舒); Luoqi (罗奇); Mi Xi Lun (米希伦); Sai Pu Ding (赛夫丁); Simcor (辛可); Su Zhi (苏之); Xi Sai (希赛); Xi Zhi Da (西之达); Xin Da Su (新达苏); Xin You Zhi (辛优宜); Xing Lu (辛露); Yixin (亿辛); Zheng Zhi (正支); Zhi Tai (旨泰); Zocor (舒降之); Cz.: Apo-Simva; Coralip; Corsim; Egilipid; Gensi; Sim; Simbela†; Simgal; Simirex; Simva†; Simvacard; Simvax; Simvor; Vabadin; Vasilip; Zocor; *Denm.*: Perichol; Simar; Simvacop†; Simvahall†; Simvahot†; Simvaklein; Simvanidda; Statstad; Vasilip; Zocor; *Fin.*: Lipcut; Zocor; *Fr.*: Lodales; Zocor; *Ger.*: BeL; Simva; SimvaAPS†; Simvabeta; Simvacard†; Simvadoc†; Simvagamma; Simvahexal†; Simvalip; Zocor; *Gr.*: Antichol; Arstatin; Avatratin; Bevostatin; Christatin; Doctiverine; Extrastatin; Glipal; Goldastatin; Iamastatin; Ipramid; Kymazol; Lepur; Lip-Down; Lipexal; Lipomin; Lipopress; Liporex; Lipozid; Lowcholid; Lusimva; Medistatin; Nezatin; Nitastin; Normotherin; Placol; Prelon; Priacin; Prizelip; Raptor; Ravostan; Redusterol; Simplaqor; Simvachol; Simvacor; Simvalark; Simvalid; Simvanox; Simvaprol; Simvasterol; Simvastil; Simvatin; Sivinar; Soneto; Sotovastin; Starezin; Stasiva; Statinal; Statinum; Stativer; Statosan; Stazor; Sterylip; Tremital; Vassor; Vastatin; Velkastatin; Veristin; Veritrat; Zocor; Zurocid; *Hong Kong*: Avastinee; Corstat; Covastin; Qualicor; Simcard; Simplaqor; Simtin; Simvacor†; Simvell; Simvor; Stavid; Vasilip; Vick-Zocostatin; Vidastat; Zocor; *Hung.*: Andever; Awestatin; Sicor; Simvacol; Simvagamma; Simvep; Simvor; Vasilip; Zocor; *India*: Biosim; Simcard; Simchol; Simlo; Simvotin; *Indon.*: Cholestat; Cholexin; Detrovel; Esvat; Ethicol; Lesvatin; Lipinorm; Mersivas; Normofat; Phalol; Pontizoc; Preschol; Rechol; Rendapid; Rocoz; Selvim; Simbado; Simchol; Simcor†; Sinova; Sintrol; Valemia; Vaster; Vazim†; Vidastat; Zaptrol; Zocor; Zovast; *Irl.*: Ritechol; Simator; Simcovas; Simtan; Simzor; Sivatin; Zocor; *Israel*: Simovil; Simvacor; Simvaxon; *Ital.*: Alpheus; Krustat; Lipenil; Liponorm; Medipo; Ornistat; Quibus; Setorilin; Simbatrix; Sinvacor; Sinvat; Sivastin; Vastgen; Xipocol; Zocor; *Malaysia*: Covastin; Lipaco; Simcard†; Simtin; Simvacor; Simvor; Stavid; Vascor; Zocor; *Mex.*: Apomastina; Colesken; Cotritev; Diskolestina; Fansia†; Imbistad; Nafatab; Nodolip; Pulsar-AT Dual; Ranvor†; Simplaqor; Sinccord; Sitatinal; Tulip†; Xintilan; Zeid; Zocor; Zorced; *Neth.*: Marsim†; Simvalip; Simvastad; Simvastaine†; Vabadin†; Zocor; *Norw.*: Zocor; *NZ*: Lipex; SimStatin; Simva; SimvaRex; *Philipp.*: Afordel; Altovast; Astin; Avastat; Buztin†; Cardiosim; Cholestad; Cholevas; Cholevast; Cholevist; Ecosta; Endovaz; Eurocor; Euvasten; Forcad; Ivast; Lipitin-S; Lipivas; Lipix; Lochol; Normastin; Orovas; Qualistat; Reduscole; Regumet; Saveor; Simbathree; Simlip; Simtin; Simvacor; Simvahex; Simvastin; Simvasyn; Simvaz; Simvoget; Sivatin; Stadex; Stavid; Stilz; Uni-Per; Vamstat; Vastat; Vastichol; Vastilan; Vazz; Vidastat; Vivastin; Wilsim; Ximvast; Zimcor; Zimvacor; Zivas; Zocor; Zolestat; Zolvastin; Zostatin; Zovast; *Pol.*: Apo-Simva; Cardin; Egilipid; Simcovas; Simgal; Simratio; Simredin†; Simvacard; Simvachol; Simvacor; Simvagen; Simvahexal; Simvalip; Simvasterol; Simvor; Vasilip; Vastan; Ximve; Zifam; Zocor; *Port.*: Actalipid†; Biolipe; Ceabisin; Ceasin†; Colvastina; Dislipina; Jabastatina; Lipaz; Simvacol; Simvasim; Sinpor; Sinvastil; Vascorim; Zapil; Zera; Zocor; *Rus.*: Actalipid (Акталипид); Aterostat (Атеростат); Cholvasim (Холвасим); Levomir (ЛевоМИР); Simgal (Симгал); Simlo (Симло); Simplacor (Симплакор); Simvacard (Симвакард); Simvacol (Симвакол); Simvahexal (Симвагексал); Simvalimit (Симвалимит); Simvastol (Симвастол); Simvor (Симвор); Synkard (Синкард); Vasilip (Вазилип); Zocor (Зокор); Zorstat (Зорстат); Zovatin (Зоватин); *S.Afr.*: Choleste; Lipidex; Michol; Redicor; Simaspen†; Simcard; Simvacor; Simvotin; Simzor; Zocor; Zysim; *Singapore*: Cholestat; Covastin; Ifistatin; Priacin; Simtin; Simvacor; Simvas; Simvor; Simzal; Vascor; Vasilip; Zocor; *Spain*: Alcosin; Arudel†; Belmalip; Colemin; Glutasey; Histop; Lipociden; Pantok; Zocor; *Swed.*: Simidon; Vabadin; Zocord; *Switz.*: Simcora; Simvasine; Simvast†; Simvastin; Zocor; *Thai.*: Bestatin; Eucor; Lochol; Simvas; Simvor; Torio; Vascor; Zimmex; Zimva; Zocor; *Turk.*: Lipovas; Simacor; Simastinteva; Simvakol; Zocor; Zovatin; *UAE*: Simvast; *UK*: Simvador; Zocor; *Ukr.*: Simgal (Симгал); Simstat (Симстат); Simvachol (Симвахол); Simvacor (СимваКОР); Simvahexal (Симвагексал)†; Simvastat (Симвастат); Simvatin (Симватин); Vabadin (Вабадин); Vasilip (Вазилип); Vasostat (Вазостат)†; Zosta (Зоста); *USA*: Zocor; *Venez.*: Cynt; Kavelor; Simplaqor; Sinvaz; Tavor; Tinasin; Vasotenal; Vastan; Zocor.

Multi-ingredient Preparations. *Arg.*: Alipas Duo; Coleflux Duo; Labistatin Duo; Redusterol Duo; Salvaxil Plus; Sinterol Compuesto; Vasotenal EZ; Vytorin; Zimetek; *Austral.*: Vytorin; *Austria*: Inegy; *Belg.*: Inegy; *Braz.*: Diocomb SI; Prevencor; Vytorin; Zetsim; *Chile*: Adacai; Vytorin; Zintrepid; *China*: Vytorin (葆至能); *Cz.*: Inegy; *Denm.*: Inegy; *Fin.*: Inegy; *Fr.*: Inegy; Vytorin; *Ger.*: Inegy; *Gr.*: Inegy; Vytorin; *Hong Kong*: Vytorin; *Hung.*: Inegy; *Indon.*: Vytorin; *Irl.*: Inegy; *Israel*: Inegy; *Ital.*: Goltor; Inegy; Vytorin; Zeklen; *Malaysia*: Vytorin; *Mex.*: Amlidual; Vytorin; Zintrepid; *Neth.*: Inegy; *Norw.*: Inegy; *NZ*: Vytorin; *Philipp.*: SafeStat; Vytorin; *Port.*: Inegy; Vytorin; *Rus.*: Inegy (Инеджи); *Singapore*: Vytorin; *Spain*: Inegy; Vytorin; *Swed.*: Inegy; *Switz.*: Inegy; *Thai.*: Vytorin; *Turk.*: Inegy; *UK*: Inegy; *USA*: Juvisync; Simcor; Vytorin; *Venez.*: Adacai; Vytorin; Zintrepid.

Pharmacopoeial Preparations
BP 2014: Simvastatin Tablets;
USP 36: Simvastatin Tablets.

Sitaxentan Sodium *(USAN, rINNM)*

Natril Sitaxentanum; Sitaxentán sódico; Sitaxentan Sodique; Sitaxsentan Sodium; TBC-11251 (sitaxentan or sitaxentan sodium); TBC-11251-z; Натрий Ситаксентан.

N-(4-Chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-o-tolyl]acetyl]-3-thiophenesulfonamide sodium.

$C_{18}H_{14}ClN_2NaO_6S_2$=476.9

CAS — 184036-34-8 (sitaxentan); 210421-74-2 (sitaxentan sodium).
UNII — 6V9JH46E20.

Uses and Administration

Sitaxentan is an endothelin receptor antagonist (p. 1245.1) with similar actions to bosentan (p. 1327.1), although it has a higher selectivity for the endothelin ET_A-receptor. It was used in the management of pulmonary hypertension functional class III (p. 1278.2) in an oral dose of 100 mg once daily, but was withdrawn due to reports of fatal liver toxicity.

Reviews.

1. Wittbrodt ET, Abubakar A. Sitaxsentan for treatment of pulmonary hypertension. *Ann Pharmacother* 2007; 41: 100–105.
2. Benedict NJ. Sitaxsentan in the management of pulmonary arterial hypertension. *Am J Health-Syst Pharm* 2007; 64: 363–8.
3. Scott LJ. Sitaxentan: in pulmonary arterial hypertension. *Drugs* 2007; 67: 761–70.

Adverse Effects

As for Bosentan, p. 1327.3. Liver toxicity, while a known adverse effect of all endothelin receptor antagonists, has been more severe with sitaxentan and it has consequently been withdrawn worldwide—see below. Increases in INR and prolongation of the prothrombin time have also been reported.

Sitaxentan is teratogenic in *rats*.

Effects on the liver. Rare, idiosyncratic and severe liver toxicity, which sometimes worsened despite stopping the drug, has been reported with sitaxentan,[1,2] and after 3 fatal cases it was withdrawn worldwide.[3,4] The EMEA announced that it would review the hepatotoxicity of the other endothelin receptor antagonists (see under Bosentan, p. 1327.3).

1. Hoeper MM, *et al.* Severe hepatitis associated with sitaxentan and response to glucocorticoid therapy. *Eur Respir J* 2009; 33: 1518–19.
2. Lavelle A, *et al.* Sitaxentan-induced hepatic failure in two patients with pulmonary arterial hypertension. *Eur Respir J* 2009; 34: 770–1.
3. EMEA. Thelin (sitaxentan) to be withdrawn due to cases of unpredictable serious liver injury (issued 10/12/10). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/f (accessed 13/01/11)
4. EMEA. Update on the withdrawal of Thelin (issued 16/12/2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/12/WC500099940.pdf (accessed 13/01/11)

Precautions

As for Bosentan, p. 1327.3. Sitaxentan is contra-indicated in patients with mild to severe hepatic impairment (Child-Pugh Class A to C).

Although, like bosentan, sitaxentan is teratogenic in *rats* and similar precautions apply, its effects on combined oral contraceptives may differ (see Interactions below).

Interactions

Sitaxentan is both an inhibitor of and a substrate for the cytochrome P450 isoenzyme CYP2C9 and interactions may therefore occur with other drugs that are either metabolised by, or inhibit, this isoenzyme. Plasma concentrations of oral anticoagulants such as warfarin may be increased.

Use with ciclosporin is contra-indicated as plasma concentrations of sitaxentan are greatly increased (see below).

Sitaxentan has increased exposure to ethinylestradiol and norethisterone in those taking oral contraceptives and may possibly increase the associated risk of thromboembolism.

Ciclosporin. Licensed product information for sitaxentan stated that its concentration was increased sixfold when given with ciclosporin 3.5 mg/kg twice daily. Although the mechanism of action is unknown, it has been postulated that sitaxentan sodium is a substrate for the organic anion transporting polypeptide (OATP) transporter protein and should therefore be used with caution with other, more potent, OATP inhibitors.

Pharmacokinetics

Peak plasma concentrations occur within 1 to 4 hours of an oral dose of sitaxentan sodium. Its absolute bioavailability is 70 to 100%. A high-fat meal delays the rate of absorption but does not affect the extent. Sitaxentan is more than 99% bound to plasma proteins, mainly albumin.

Sitaxentan is highly metabolised by the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 to weakly active metabolites. About 50 to 60% of a dose is excreted in the urine with the remainder appearing in the faeces; less than 1% is excreted unchanged. Sitaxentan has a terminal elimination half-life of 10 hours and steady state is achieved within about 6 days.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Thelin†; *Austria*: Thelin†; *Belg.*: Thelin†; *Canad.*: Thelin†; *Cz.*: Thelin†; *Denm.*: Thelin†; *Fr.*: Thelin†; *Ger.*: Thelin†; *Gr.*: Thelin†; *Irl.*: Thelin†; *Ital.*: Thelin†; *Neth.*: Thelin†; *Port.*: Thelin†; *Spain*: Thelin†; *Swed.*: Thelin†; *UK*: Thelin†.

Sodium Apolate *(BAN, rINN)*

Apolate de Sodium; Apolato de sodio; Lyapolate Sodium (USAN); Natrii Apolas; Natriumapolaatti; Natriumapolat; Sodium Lyapolate; Натрия Аполат.

Poly(sodium ethylenesulphonate).

$(C_2H_3NaO_3S)_n$

CAS — 25053-27-4.

ATC — C05BA02.

ATC Vet — QC05BA02.

UNII — 946140SD9F.

Profile

Sodium apolate is a synthetic heparinoid anticoagulant. It has been used in the topical treatment of haematomas and superficial thromboses and for the relief of sprains and contusions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Pergalen.

Sodium Nitroprusside

Disodium (OC-6-22)-Pentakis(cyano-C)nitrosylferrate Dihydrate; Natrii Nitroprussias; Natrii Nitroprussias Dihydricus; Natrii Nitroprussicum; Natrio nitroprusidas; Natriumnitroprussid; Natriumnitroprussidi; Nitroprusiato sódico; Nitroprussid sodný dihydrát; Nitroprussidnatrium; Nitroprusszidnátrium; Sodium Nitroferricyanide Dihydrate; Sodium Nitroprussiate; Sodium, nitroprussiate de; Sodu nitroprusydek; Sodyum Nitroprusid; Нитропруссид Натрия.

Sodium nitrosylpentacyanoferrate(III) dihydrate.

$Na_2Fe(CN)_5NO,2H_2O$=298.0

CAS — 14402-89-2 (anhydrous sodium nitroprusside); 13755-38-9 (sodium nitroprusside dihydrate).

ATC — C02DD01.

ATC Vet — QC02DD01.

UNII — EAO03PE1TC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Sodium Nitroprusside). Reddish-brown crystals or powder. Freely soluble in water; slightly soluble in alcohol. Protect from light.

USP 36: (Sodium Nitroprusside). Reddish-brown, practically odourless crystals or powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; insoluble in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Sodium nitroprusside has been reported to be visually incompatible with cisatracurium besilate[1] and with levofloxacin[2] during simulated Y-site administration.

1. Trissel LA, *et al.* Compatibility of cisatracurium besylate with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1997; 54: 1735–41.
2. Saltsman CL, *et al.* Compatibility of levofloxacin with 34 medications during simulated Y-site administration. *Am J Health-Syst Pharm* 1999; 56: 1458–9.

Stability in solution. Solutions of sodium nitroprusside decompose when exposed to light and must be protected during infusion by wrapping the container with aluminium foil or some other light-proof material. Nitroprusside will react with minute quantities of organic and inorganic substances forming highly coloured products. If this occurs the solution should be discarded. Solutions should not be used more than 24 hours after preparation.

The instability of sodium nitroprusside solutions has been the subject of considerable investigation. Although stated to be more stable in acid than in alkaline solution,[1] a later study[2] found that whereas the initial light-induced darkening of a 1% solution was independent of pH, further degradation leading to the development of a blue precipitate required an acid pH. If protected from light by wrapping in aluminium foil, sodium nitroprusside 50 or 100 micrograms/mL was found to be stable in 5% glucose, lactated Ringer's, and normal saline solutions for 48 hours.[3] In clinical practice the infusion container should be opaque or protected with foil, but an amber giving set may be used, to allow visual monitoring.[4,5]

Various substances have been reported to increase the stability of nitroprusside solutions, including dimethyl sulfoxide,[6] glycerol,[1] sodium citrate,[1] and other salts with anionic chelating potential such as sodium acetate or phosphate.[1] In contrast sodium bisulfite and the hydroxybenzoates are reported to reduce stability.[1]

1. Schumacher GE. Sodium nitroprusside injection. *Am J Hosp Pharm* 1966; 23: 532.
2. Hargrave RE. Degradation of solutions of sodium nitroprusside. *J Hosp Pharm* 1974; 32: 188–91.
3. Mahony C, *et al.* In vitro stability of sodium nitroprusside solutions for intravenous administration. *J Pharm Sci* 1984; 73: 838–9.
4. Davidson SW, Lyall D. Sodium nitroprusside stability in light-protective administration sets. *Pharm J* 1987; 239: 599–601.
5. Lyall D. Sodium nitroprusside stability. *Pharm J* 1988; 240: 5.
6. Asker AF, Gragg R. Dimethyl sulfoxide as a photoprotective agent for sodium nitroprusside solutions. *Drug Dev Ind Pharm* 1983; 9: 837–48.

Uses and Administration

Sodium nitroprusside is a short-acting hypotensive drug with a duration of action of 1 to 10 minutes. It produces peripheral vasodilatation and reduces peripheral resistance by a direct action on both veins and arterioles. It has been termed a nitrovasodilator because it releases nitric oxide *in vivo*. Its effects appear within a few seconds of intravenous infusion. Sodium nitroprusside is used in the treatment of hypertensive crises (p. 1251.1) and to produce controlled hypotension during general anaesthesia. It has also been used to reduce preload and afterload in severe heart failure (p. 1262.3) including that associated with myocardial infarction (p. 1257.1).

It is given by continuous intravenous infusion of a solution containing 50 to 200 micrograms/mL. A controlled infusion device must be used. The solution should be prepared immediately before use by dissolving sodium nitroprusside in glucose 5% and then diluting with glucose 5%; the solution must be protected from light during infusion. Blood pressure should be monitored closely and care should be taken to prevent extravasation. In general, treatment should not continue for more than 72 hours. If required for several days, concentrations of cyanide should be monitored; the blood concentration should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. Thiocyanate concentrations in blood should also be measured if infusion continues for more than 72 hours and should not exceed 100 micrograms/mL. Since rebound hypertension has been reported when sodium nitroprusside is withdrawn, the infusion should be tailed off gradually over 10 to 30 minutes.

For **hypertensive crises** in patients not receiving antihypertensive drugs, an initial dose of 0.3 to 1.5 micrograms/kg per minute may be given, increasing gradually under close supervision until the desired reduction in blood pressure is achieved. The average dose required to maintain the blood pressure 30 to 40% below the pretreatment diastolic blood pressure is 3 micrograms/kg per minute and the usual dose range is 0.5 to 6 micrograms/kg per minute. Lower doses should be used in patients already receiving other antihypertensives. The maximum recommended rate is about 8 micrograms/kg per minute in the UK, and 10 micrograms/kg per minute in the USA; infusions at these rates should be used for no longer than 10 minutes and should be stopped after 10 minutes if there is no response. If there is a response, sodium nitroprusside should ideally be given for only a few hours to avoid the risk of cyanide toxicity. Treatment with an oral antihypertensive should be introduced as soon as possible.

For the **induction of hypotension** during anaesthesia a maximum dose of 1.5 micrograms/kg per minute is recommended.

In **heart failure** an initial dose of 10 to 15 micrograms/minute has been used, increasing by 10 to 15 micrograms/minute every 5 to 10 minutes according to response. The usual dosage range is 10 to 200 micrograms/minute.

Sodium nitroprusside has also been used as a reagent for detecting ketones in urine.

Administration in children. Although experience is more limited than with adults, sodium nitroprusside has been successfully used in infants and children. Continuous infusion of nitroprusside at a rate of 2 to 4 micrograms/kg per minute for 28 days was reported[1] in an 11-year-old child with refractory hypertension, without any signs of thiocyanate toxicity. In a series of 58 neonates with cardiovascular disorders or respiratory distress syndrome,[2] sodium nitroprusside was given in a usual initial dose of 250 to 500 nanograms/kg per minute, and the rate was then repeatedly doubled at intervals of 15 to 20 minutes until the desired effect was achieved, adverse effects supervened, or it was judged ineffective. The maximum rate did not exceed 6 micrograms/kg per minute. Infusion of sodium nitroprusside in doses of 0.5 to 8 micrograms/kg per minute to produce controlled reduction of blood pressure has also been reported[3] in 28 children with hypertensive crises; 16 had also received labetalol.[3] The risks of toxicity in paediatric patients have been reviewed.[4,5] One review[4] of sodium nitroprusside use in paediatric surgical patients found that infusions of 1.8 micrograms/kg or more per minute were associated with a greater risk of cyanide toxicity.

Although sodium nitroprusside is unlicensed in the UK for use in children, the *BNFC* suggests that neonates, infants, and children may be given an initial continuous intravenous infusion of 500 nanograms/kg per minute, which may be increased in steps of 200 nanograms/kg per minute to a maximum of 8 micrograms/kg per minute (or a maximum of 4 micrograms/kg per minute if given for longer than 24 hours).

For the use of inhaled sodium nitroprusside in neonates with pulmonary hypertension see below.

1. Luderer JR, *et al.* Long-term administration of sodium nitroprusside in childhood. *J Pediatr* 1977; 91: 490–1.
2. Benitz WE, *et al.* Use of sodium nitroprusside in neonates: efficacy and safety. *J Pediatr* 1985; 106: 102–10.
3. Deal JE, *et al.* Management of hypertensive emergencies. *Arch Dis Child* 1992; 67: 1089–92.
4. Moffett BS, Price JF. Evaluation of sodium nitroprusside toxicity in pediatric cardiac surgical patients. *Ann Pharmacother* 2008; 42: 1600–4.
5. Thomas C, *et al.* Sodium-nitroprusside-induced cyanide toxicity in pediatric patients. *Expert Opin Drug Safety* 2009; 8: 599–602.

Ergotamine poisoning. For the use of sodium nitroprusside in the treatment of cyanosis of the extremities due to ergotamine overdosage, see Cardiovascular Effects, p. 674.3.

Pulmonary hypertension. Inhaled sodium nitroprusside has been used[1,2] as an alternative to inhaled nitric oxide in the treatment of hypoxic neonates with pulmonary hypertension (p. 1278.2).

1. Palhares DB, *et al.* Endotracheal inhalatory sodium nitroprusside in severely hypoxic newborns. *J Perinat Med* 1998; 26: 219–24.
2. Mestan KKL, *et al.* Cardiopulmonary effects of nebulized sodium nitroprusside in term infants with hypoxic respiratory failure. *J Pediatr* 2003; 143: 640–3.

Adverse Effects

Sodium nitroprusside rapidly reduces blood pressure and is converted in the body to cyanide and then thiocyanate. Its adverse effects can be attributed mainly to excessive hypotension and excessive cyanide accumulation; thiocyanate toxicity may also occur, especially in patients with renal impairment. Intravenous infusion of sodium nitroprusside may produce nausea and vomiting, apprehension, headache, dizziness, restlessness, perspiration, palpitations, retrosternal discomfort, abdominal pain, and muscle twitching, but these effects may be reduced by slowing the infusion rate.

An excessive amount of cyanide in plasma (more than 80 nanograms/mL), because of overdosage or depletion of endogenous thiosulfate (which converts cyanide to thiocyanate *in vivo*), may result in tachycardia, sweating, hyperventilation, arrhythmias, and profound metabolic acidosis. Metabolic acidosis may be the first sign of cyanide toxicity. Methaemoglobinaemia may also occur.

Adverse effects attributed to thiocyanate include headache, tinnitus, miosis, arthralgia, muscle cramps, and hyperreflexia; confusion, hallucinations, and convulsions have also been reported.

Other adverse effects include thrombocytopenia and phlebitis.

Effects on the blood. *THROMBOCYTOPENIA.* Platelet counts decreased in 7 of 8 patients with heart failure 1 to 6 hours after intravenous infusion of nitroprusside was started.[1] The counts began to return to normal 24 hours after the infusion was stopped.

1. Mehta P, *et al.* Nitroprusside lowers platelet count. *N Engl J Med* 1978; 299: 1134.

Effects on the gastrointestinal tract. Five out of 38 patients who were given sodium nitroprusside intravenously for controlled hypotension during surgery developed symptoms of adynamic ileus postoperatively.[1] The symptoms could have been secondary to intestinal ischaemia due to diminished mesenteric arterial blood flow. However, other explanations have been proposed including sympathetic stimulation[2,3] or the concomitant use of opioid analgesics.[4]

1. Chen JW, *et al.* Adynamic ileus following induced hypotension. *JAMA* 1985; 253: 633.
2. Gelman S. Adynamic ileus following induced hypotension. *JAMA* 1985; 254: 1721.
3. Lampert BA. Adynamic ileus following induced hypotension. *JAMA* 1985; 254: 1721.
4. Lemmo J, Karnes J. Adynamic ileus following induced hypotension. *JAMA* 1985; 254: 1721.

Effects on intracranial pressure. A significant increase in intracranial pressure while the mean blood pressure was 80 or 90% of initial values was reported[1] in 14 normocapnic patients given an infusion of sodium nitroprusside to

produce controlled hypotension before neurosurgery; values reverted towards normal at mean blood pressures of 70% of controls. A similar but insignificant trend occurred in 5 hypocapnic patients. In another report[2] a rise in intracranial pressure was noted after the use of nitroprusside in a patient with Reye's syndrome.

1. Turner JM, *et al.* Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *Br J Anaesth* 1977; 49: 419–24.
2. Griswold WR, *et al.* Nitroprusside-induced intracranial hypertension. *JAMA* 1981; 246: 2679–80.

Phlebitis. Acute transient phlebitis has occurred after infusion of sodium nitroprusside.[1]

1. Miller R, Stark DCC. Acute phlebitis from nitroprusside. *Anesthesiology* 1978; 49: 372.

Treatment of Adverse Effects

Adverse effects due to excessive hypotension may be treated by slowing or stopping the infusion.

For details of the treatment of cyanide poisoning see Hydrocyanic Acid, p. 2156.2. Thiocyanate can be removed by dialysis.

Precautions

Sodium nitroprusside should not be used in the presence of compensatory hypertension (for example, in arteriovenous shunts or coarctation of the aorta). It should be used with caution, if at all, in patients with hepatic impairment, and in patients with low plasma-cobalamin concentrations or Leber's optic atrophy. It should also be used with caution in patients with impaired renal or pulmonary function and with particular caution in patients with impaired cerebrovascular circulation. Thiocyanate, a metabolite of sodium nitroprusside, inhibits iodine binding and uptake and sodium nitroprusside should be used with caution in patients with hypothyroidism. The blood-thiocyanate concentration should be monitored if treatment continues for more than 3 days and should not exceed 100 micrograms/mL although toxicity may be apparent at lower thiocyanate concentrations. Thiocyanate concentrations do not reflect cyanide toxicity and cyanide concentrations should also be monitored; the blood concentration of cyanide should not exceed 1 microgram/mL and the serum concentration should not exceed 80 nanograms/mL. The acid–base balance should also be monitored. Care should be taken to ensure that extravasation does not occur. Sodium nitroprusside should not be withdrawn abruptly due to the risk of rebound effects.

Aortic stenosis. Vasodilators such as sodium nitroprusside are usually contra-indicated in conditions where cardiac outflow is obstructed since cardiac output cannot increase to compensate for the fall in blood pressure. However, a study[1] in patients with aortic stenosis and severe left ventricular dysfunction found that sodium nitroprusside was well tolerated and that it rapidly and markedly improved cardiac function.

1. Khot UN, *et al.* Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med* 2003; 348: 1756–63.

Pregnancy. Although there are concerns that nitroprusside given to the mother might produce cyanide toxicity in the fetus, a systematic review[1] was unable to find sufficient evidence to determine the risk.

1. Sass N, *et al.* Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007; 125: 108–11.

Tachyphylaxis. Tachyphylaxis to sodium nitroprusside was associated with high plasma concentrations of cyanide without metabolic acidosis in 3 patients undergoing hypotensive anaesthesia.[1]

1. Cottrell JE, *et al.* Nitroprusside tachyphylaxis without acidosis. *Anesthesiology* 1978; 49: 141–2.

Withdrawal. Rebound haemodynamic changes, including hypertension and increased heart rate, occurred 10 to 30 minutes after stopping intravenous sodium nitroprusside infusion in 20 patients with heart failure.[1] The changes generally resolved spontaneously within 1 to 3 hours and produced only minimal exacerbation of symptoms in most patients, although 3 developed pulmonary oedema 20 to 30 minutes after stopping the infusion, needing restarting of nitroprusside in 2 cases. A study[2] investigating a possible mechanism for this effect found that plasma-renin concentrations were increased during infusion of nitroprusside and remained elevated for 30 minutes after the infusion was stopped. It was suggested that this persistence of elevated plasma-renin concentrations after clearance of short-lived nitroprusside may be responsible for the rebound effects.

1. Packer M, *et al.* Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. *N Engl J Med* 1979; 301: 1193–7.
2. Cottrell JE, *et al.* Rebound hypertension after sodium nitroprusside-induced hypotension. *Clin Pharmacol Ther* 1980; 27: 32–6.

Interactions

Enhanced hypotension should be expected if sodium nitroprusside is used with other antihypertensives or drugs that produce hypotension.

Alteplase. Sodium nitroprusside infusion prolonged the fibrinolytic activity of alteplase when given to *animals*; use of nitrovasodilators with alteplase may be responsible for the enhanced bleeding tendency seen in some patients on thrombolytic therapy.[1]

1. Kochut R, *et al.* Prolongation of fibrinolytic activity of tissue plasminogen activator by nitrovasodilators. *Lancet* 1990; 335: 669.

Pharmacokinetics

Sodium nitroprusside is rapidly metabolised to cyanide in erythrocytes and smooth muscle and, *in vivo*, this is followed by the release of nitric oxide, the active metabolite. Cyanide is further metabolised in the liver to thiocyanate, which is slowly excreted in the urine; this metabolism is mediated by the enzyme rhodanase and requires the presence of thiosulfate. The plasma half-life of thiocyanate is reported to be about 3 days, but may be much longer in patients with renal impairment.

Reviews.

1. Schulz V. Clinical pharmacokinetics of nitroprusside, cyanide, thiosulphate and thiocyanate. *Clin Pharmacokinet* 1984; 9: 239–51.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Doketrol; Niprusodio; Nitroprus; *Braz.*: Nipride; Nitropresabbott; Nitroprus; *Canad.*: Nipride; *Cz.*: Nipruss; *Fr.*: Nitriate; *Ger.*: Nipruss; *Gr.*: Nitriate; *India*: Nipress; Sonide; *Israel*: Nipruss; *Jpn*: Nitopro; *Rus.*: Naniprus (Нанипрус); *S.Afr.*: Hypoten; SNP†; *Spain*: Nitroprusslat; *Turk.*: Nipruss; *USA*: Nitropress.

Pharmacopoeial Preparations
BP 2014: Sodium Nitroprusside Infusion;
USP 36: Sodium Nitroprusside for Injection.

Sotalol Hydrochloride

(BANM, USAN, rINNM) ⊗

d,l-Sotalol Hydrochloride; Hidrocloruro de sotalol; MJ-1999; Sotalol, chlorhydrate de; Sotalol, hidrocloruro de; Sotalol Hidroklorür; Sotalolhydrochlorid; Sotalol-hydrochlorid; Sotalolhydroklorid; Sotalolí Hydrochloridum; Sotalolihydrokloridi; Sotalolio hidrochloridas; Szotalol-hidroklorid; Соталола Гидрохлорид.

4′-(1-Hydroxy-2-isopropylaminoethyl)methanesulphonanilide hydrochloride.

$C_{12}H_{20}N_2O_3S,HCl$=308.8

CAS — 3930-20-9 (sotalol); 959-24-0 (sotalol hydrochloride).

ATC — C07AA07.

ATC Vet — QC07AA07.

UNII — HEC37C70XX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Sotalol Hydrochloride). A white or almost white powder. Freely soluble in water; soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 4.0 to 5.0. Protect from light.

USP 36: (Sotalol Hydrochloride). A white to off-white powder. Freely soluble in water; soluble in alcohol; very slightly soluble in chloroform.

Stability. Suspensions of sotalol hydrochloride 5 mg/mL made using either commercially available or extemporaneously prepared vehicles were found[1] to be stable for up to 3 months when stored at 4 degrees or 25 degrees. Prolonged storage at 25 degrees was not recommended, however, because of the risk of microbial growth.

1. Nahata MC, Morosco RS. Stability of sotalol in two liquid formulations at two temperatures. *Ann Pharmacother* 2003; 37: 506–9.

Uses and Administration

Sotalol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack both intrinsic sympathomimetic and membrane-stabilising properties. In addition to the class II antiarrhythmic activity of beta blockers, sotalol lengthens the duration of the action potential resulting in class III antiarrhythmic activity. For a classification and explanation of antiarrhythmic activity, see p. 1243.1.

Sotalol is used in the management of ventricular and supraventricular arrhythmias (p. 1266.1). Because of its proarrhythmic effects, it is usually reserved for severe or life-threatening arrhythmias, and it should not be used in patients with asymptomatic ventricular arrhythmias. Although it was formerly used for its beta-blocking effects in the management of angina pectoris, hypertension, and myocardial infarction, it is no longer recommended for these indications because of the risk of precipitating arrhythmias.

Sotalol is given as the hydrochloride. Treatment should be started in hospital with suitable monitoring facilities. The QT interval should be assessed before the start of treatment and whenever the dosage is adjusted (see Precautions p. 1499.2); plasma-electrolyte concentrations and renal function should also be monitored. The dose should be reduced in patients with renal impairment (see p. 1499.1).

The usual initial oral dose of sotalol hydrochloride is 80 mg daily, as a single dose or in two divided doses. The dosage is then individualised according to response, and doses are increased gradually allowing 2 or 3 days between increments. US licensed product information recommends a higher initial dose of 80 mg twice daily and this should not be increased for at least 3 days. Most patients respond to doses of 160 to 320 mg daily (usually given in two divided doses). Some patients with ventricular arrhythmias may require doses as high as 640 mg daily.

Sotalol may be given intravenously to control acute arrhythmias, to substitute for oral therapy, and for programmed electrical stimulation. To control acute arrhythmias, sotalol hydrochloride is given in a dose of 20 to 120 mg (500 to 1500 micrograms/kg) intravenously over 10 minutes. This dose may be repeated every 6 hours if necessary. To substitute for oral therapy an intravenous infusion of 200 to 500 micrograms/kg per hour may be used. The total daily dose should not exceed 640 mg. (In the USA, a dose of 75 mg infused over 5 hours is recommended to replace an oral dose of 80 mg.) For programmed electrical stimulation (to test antiarrhythmic efficacy) an initial dose of 1.5 mg/kg is given over 10 to 20 minutes, followed by an intravenous infusion of 200 to 500 micrograms/kg per hour.

Sotalol is used as a racemic mixture; *d*-sotalol (dexsotalol; (+)-sotalol) has also been investigated as an antiarrhythmic but development was stopped when it was found to increase mortality (see Action, below).

General references.

1. Fitton A, Sorkin EM. Sotalol: an updated review of its pharmacological properties and therapeutic use in cardiac arrhythmias. *Drugs* 1993; 46: 678–719.
2. Nappi JM, McCollam PL. Sotalol: a breakthrough antiarrhythmic? *Ann Pharmacother* 1993; 27: 1359–68.
3. Zanetti LAF. Sotalol: a new class III antiarrhythmic agent. *Clin Pharm* 1993; 12: 883–91.
4. Hohnloser SH, Woosley RL. Sotalol. *N Engl J Med* 1994; 331: 31–8.
5. Anderson JL, Prystowsky EN. Sotalol: an important new antiarrhythmic. *Am Heart J* 1999; 137: 388–409.
6. Chaki AL, *et al.* Sotalol as adjunctive therapy to implantable cardioverter-defibrillators in heart failure patients. *Congest Heart Fail* 2009; 15: 144–7.

Action. Sotalol is used as the racemic mixture of the two stereoisomers, *d*-sotalol (dexsotalol; (+)-sotalol) and *l*-sotalol ((-)-sotalol). A comparison of the effects of *d*-sotalol and racemic sotalol in 6 healthy subjects[1] showed that the beta-blocking activity resided almost entirely in the *l*-isomer, while the effects on the QT interval, which are consistent with type III antiarrhythmic activity, appear to be due to both isomers. A study in 8 healthy subjects also showed a lack of beta blockade by *d*-sotalol.[2] This would suggest that the electrophysiological effects of sotalol are unrelated to its beta-blocking properties. *d*-Sotalol has been investigated as an antiarrhythmic.[3] However, a preliminary placebo-controlled study in patients with myocardial infarction at high risk of arrhythmia due to impaired left ventricular function was terminated early when increased mortality was seen in the treatment group.[4,5]

1. Johnston GD, *et al.* A comparison of the cardiovascular effects of (+)-sotalol and (±)-sotalol following intravenous administration in normal volunteers. *Br J Clin Pharmacol* 1985; 20: 507–10.
2. Yasuda SU, *et al.* d-Sotalol reduces heart rate in vivo through a β-adrenergic receptor-independent mechanism. *Clin Pharmacol Ther* 1993; 53: 436–42.
3. Advani SV, Singh BN. Pharmacodynamic, pharmacokinetic and antiarrhythmic properties of d-sotalol, the dextro-isomer of sotalol. *Drugs* 1995; 49: 664–79.
4. Choo V. SWORD slashed. *Lancet* 1994; 344: 1358.
5. Waldo AL, *et al.* Effect of d-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. *Lancet* 1996; 348: 7–12. Correction. *ibid.*; 416.

Administration. Reference to the development of an intravenous dosage regimen for sotalol.[1]

1. Somberg JC, *et al.* Developing a safe intravenous sotalol dosing regimen. *Am J Ther* 2010; 17: 365–72.

Administration in children. Sotalol has been used to treat both ventricular and supraventricular arrhythmias in children aged from newborn to adolescent;[1-3] it appears to be effective and well-tolerated, although proarrhythmic effects may occur. Neonates may be more sensitive to the QT-prolonging effects of sotalol[3] and lower doses may be appropriate. In the UK, the *BNFC* recommends the following oral doses of sotalol hydrochloride:

- Neonates: initial dose 1 mg/kg twice daily, increased as necessary every 3 to 4 days to a maximum of 4 mg/kg twice daily

- Children aged 1 month to 12 years: initial dose 1 mg/kg twice daily, increased as necessary every 2 to 3 days to a maximum of 4 mg/kg twice daily (maximum total dose 80 mg twice daily)

Licensed product information in the USA recommends doses of sotalol hydrochloride based on body surface area. Children aged 2 years and over may be given an initial dose of 30 mg/m² three times daily, increased as necessary at intervals of at least 36 hours to a maximum of 60 mg/m² three times daily. For children under 2 years of age the dose should be further reduced, and nomograms are available providing age-specific recommendations.

In children with refractory supraventricular tachycardia, sotalol has been given with flecainide; in a study[4] in children aged under 1 year, doses used ranged from 100 to 250 mg/m² daily of sotalol and from 40 to 150 mg/m² daily of flecainide.

Sotalol has also been used transplacentally to treat fetal tachycardias, including atrial flutter and supraventricular tachycardia. It may be effective as second-line therapy in addition to digoxin,[5] and has also been used first-line.[6,7] However, one retrospective study[6] of 21 fetuses given sotalol transplacentally found that it was more effective in atrial flutter than in supraventricular tachycardia; mortality was also higher in fetuses with supraventricular tachycardia, and the authors therefore suggested that sotalol should only be used in resistant cases.

1. Çeliker A, *et al.* Sotalol in treatment of pediatric cardiac arrhythmias. *Pediatr Int* 2001; **43**: 624–30.
2. Beaufort-Krol GCM, Bink-Boelkens MTE. Effectiveness of sotalol for atrial flutter in children after surgery for congenital heart disease. *Am J Cardiol* 1997; **79**: 92–4.
3. Läer S, *et al.* Development of a safe and effective pediatric dosing regimen for sotalol based on population pharmacokinetics and pharmacodynamics in children with supraventricular tachycardia. *J Am Coll Cardiol* 2005; **46**: 1322–30.
4. Price JF, *et al.* Flecainide and sotalol: a new combination therapy for refractory supraventricular tachycardia in children <1 year of age. *J Am Coll Cardiol* 2002; **39**: 517–20.
5. Sonesson S-E, *et al.* Foetal supraventricular tachycardia treated with sotalol. *Acta Paediatr* 1998; **87**: 584–7.
6. Oudijk MA, *et al.* Sotalol in the treatment of fetal dysrhythmias. *Circulation* 2000; **101**: 2721–6.
7. Rebelo M, *et al.* Sotalol in the treatment of fetal tachyarrhythmia. *Rev Port Cardiol* 2006; **25**: 477–81.

Administration in renal impairment. Sotalol is excreted mainly unchanged by the kidneys and may accumulate in renal impairment. The usual daily dosage (see Uses and Administration, p. 1498.2) should therefore be reduced, either by decreasing the size of each dose, or by increasing the interval between doses. UK licensed product information for oral or intravenous sotalol recommends the following doses based on creatinine clearance (CC):

- CC 30 to 60 mL/minute: half usual dose
- CC 10 to 30 mL/minute: quarter usual dose
- CC less than 10 mL/minute: not recommended

Oral dosage recommendations in the USA depend on both the indication and CC, and incremental increases should not be made until 5 or 6 doses have been given. In the treatment of ventricular arrhythmias, licensed product information recommends that in renal impairment doses should be given at the following intervals:

- CC 30 to 59 mL/minute: every 24 hours
- CC 10 to 29 mL/minute: every 36 to 48 hours
- CC less than 10 mL/minute: dosage should be individualised

For the treatment of atrial fibrillation, the same dosage intervals are recommended but sotalol is contra-indicated if CC is less than 40 mL/minute.

In patients who require intravenous sotalol hydrochloride, US recommendations are that the dosage frequency be reduced to once daily in those with CC between 60 and 40 mL/minute; a recommended initial dose is 75 mg daily, infused over 5 hours. It should be avoided completely (regardless of indication) in those with CC less than 40 mL/minute.

In a study of 10 hypertensive patients with varying degrees of renal impairment,[1] the apparent first-order elimination rate constant and plasma clearance of oral sotalol correlated with glomerular filtration rate. Another study[2] compared the kinetics of oral sotalol in patients with normal renal function, renal impairment, and renal failure. Elimination half-lives of 8.1 and 24.2 hours were reported in patients with CC above 39 mL/minute and between 8 and 38 mL/minute, respectively. It was suggested that an increase in the dosage interval to 48 or 72 hours may be necessary to compensate for longer half-lives. Caution is required when sotalol is used in patients on dialysis; a half-life of 33.9 hours was reported in patients with renal failure but this fell to 5.8 hours during dialysis which removed about 43% of sotalol.

1. Berglund G, *et al.* Pharmacokinetics of sotalol after chronic administration to patients with renal insufficiency. *Eur J Clin Pharmacol* 1980; **18**: 321–6.
2. Blair AD, *et al.* Sotalol kinetics in renal insufficiency. *Clin Pharmacol Ther* 1981; **29**: 457–63.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Torsade de pointes has been reported in patients given sotalol, usually due to prolongation of the QT interval. The QT interval should be monitored: extreme caution is required if the QT interval exceeds 500 milliseconds and sotalol should be stopped or the dose reduced if the QT interval exceeds 550 milliseconds. As hypokalaemia or hypomagnesaemia may predispose patients to arrhythmias, serum-electrolyte concentrations should be monitored before and during treatment with sotalol.

Sotalol should be used with caution in renal impairment (see under Uses and Administration, above) and is contra-indicated in patients whose creatinine clearance is less than 10 mL/minute.

Breast feeding. Sotalol is distributed into breast milk and milk to serum ratios have been reported[1-3] to range from 2.2 to 8.8. In one report[2] it was calculated that a breast-fed infant might ingest 20 to 23% of a maternal dose; however, no bradycardia was noted in the infant in this study. The American Academy of Pediatrics states[4] that there have been no reports of clinical effects in breast-fed infants whose mothers were receiving sotalol and that therefore it may be considered to be usually compatible with breast feeding.

1. O'Hare MF, *et al.* Sotalol as a hypotensive agent in pregnancy. *Br J Obstet Gynaecol* 1980; **87**: 814–20.
2. Hackett LP, *et al.* Excretion of sotalol in breast milk. *Br J Clin Pharmacol* 1990; **29**: 277–8.
3. Wagner X, *et al.* Coadministration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk. *Am Heart J* 1990; **119**: 700–2.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *Ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sotalol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

There is an increased risk of precipitating ventricular arrhythmias if sotalol is given with other drugs that prolong the QT interval, and use with the following drugs is therefore not recommended: class Ia antiarrhythmics (including disopyramide, procainamide, and quinidine), amiodarone, phenothiazine antipsychotics, tricyclic antidepressants, certain antihistamines (astemizole or terfenadine), cisapride, erythromycin, halofantrine, pentamidine, quinolones, sultopride, and vincamine. Caution is required if sotalol is given with drugs that cause electrolyte disturbances, such as diuretics, since this also increases the risk of arrhythmias.

Other interactions associated with beta blockers are discussed on p. 1321.2.

Pharmacokinetics

Sotalol is almost completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 to 4 hours after a dose. The plasma elimination half-life is about 10 to 20 hours. Sotalol has low lipid solubility. Very little is metabolised and it is excreted unchanged in the urine. Binding to plasma proteins is reported to be low. It crosses the placenta and is distributed into breast milk; concentrations in milk may be higher than those in maternal serum (see Breast Feeding, above). Only small amounts are reported to cross the blood-brain barrier and enter the CSF. Sotalol is removed by dialysis.

General references.

1. Singh BN, *et al.* Sotalol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use. *Drugs* 1987; **34**: 311–49.

Pregnancy. The systemic clearance of sotalol in 6 healthy women after an intravenous dose was significantly higher during pregnancy than in the postnatal period, and the mean elimination half-life was shorter (6.6 versus 9.3 hours), although the latter difference was not significant.[1] Clearance after an oral dose was also higher during pregnancy than afterwards, but half-lives (10.9 versus 10.3 hours) and mean bioavailability were similar. The changes were probably due to alterations in renal function in the antenatal period.

In a study[2] of transplacental therapy, sotalol was found to cross the placenta easily and completely, with steady-state plasma concentrations similar in mother and fetus. Sotalol accumulated in the amniotic fluid but not in the fetus; it was not associated with fetal growth restriction.

1. O'Hare MF, *et al.* Pharmacokinetics of sotalol during pregnancy. *Eur J Clin Pharmacol* 1983; **24**: 521–4.
2. Oudijk MA, *et al.* Treatment of fetal tachycardia with sotalol: transplacental pharmacokinetics and pharmacodynamics. *J Am Coll Cardiol* 2003; **42**: 765–70.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sotacor; *Austral.*: Cardol; Solavert; Sotacor; Sotahexal†; *Austria*: Sotacor; Sotahexal; Sotamed; Sotastad; *Belg.*: Sotalex; *Braz.*: Sotacor; Sotahexal; *Canad.*: Rylosol; *Chile*: Hipecor; *China*: Ji Di (济迪); Jin Lv Xin (金缕欣); Sotacor (施太可); Tan Shi (坦释); Wei Te (伟特); Xi An Lin (喜安林); Yi Huan (伊缓); Yuan Qi (元齐); *Cz.*: Sotahexal; Sotalex†; *Fin.*: Sotacor; Sotalin†; *Fr.*: Sotalex; *Ger.*: Darob†; Jutalex†; Rentibloc; Sota-Puren†; Sota-saar†; Sota†; Sotabeta; Sotagamma; Sotahexal†; Sotalex; Sotalodoc†; Sotastad†; *Gr.*: Sotalex; *Hong Kong*: Sotacor†; *Hung.*: Sotahexal; Sotalex; *Irl.*: Sotacor; Sotoger; *Ital.*: Rytmobeta; Sotalex; *Jpn*: Sotacor; *Malaysia*: Sotacor; *Mex.*: Sotaper; *Neth.*: Sotacor†; *Norw.*: Sotacor†; *NZ*: Sotacor; Sotahexal†; *Philipp.*: Sotalex†; *Pol.*: Biosotal; Darob; Sotahexal; *Port.*: Darob; *Rus.*: Sotahexal (Соталекан); Sotalex (Соталекс); *S.Afr.*: Sotacor; Sotahexal; *Singapore*: Sotacor; SotaHexal; *Spain*: Sotapor; *Swed.*: Sotacor; *Switz.*: Sotalex; *Turk.*: Darob; Sotarit; Talozin; *UK*: Beta-Cardone; Sotacor; *Ukr.*: Soritmik (Соритмік); Sotahexal (Соталекан)†; *USA*: Betapace.

Multi-ingredient Preparations. *S.Afr.*: Sotazide†.

Pharmacopoeial Preparations

BP 2014: Sotalol Injection; Sotalol Tablets;
USP 36: Sotalol Hydrochloride Oral Suspension; Sotalol Hydrochloride Tablets.

Spirapril Hydrochloride *(BANM, USAN, rINNM)*

Espirapril, hidrocloruro de; Hidrocloruro de espirapril; Sch-33844; Spirapriilhydrokloridi; Spirapril, Chlorhydrate de; Spirapril-hydrochlorid; Spirapriihydroklorid; Spiraprili hydrochloridum; Spirapriilio hidrochloridas; TI-211-950; Спираприла Гидрохлорид.

(*S*)-7-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid hydrochloride.

$C_{22}H_{30}N_2O_5S_2$,HCl=503.1.

CAS — 83647-97-6 (spirapril); 94841-17-5 (spirapril hydrochloride).

ATC — C09AA11.

ATC Vet — QC09AA11.

UNII — OCC2SLM897.

Pharmacopoeias. *Eur.* (see p. vii) includes the monohydrate.

Ph. Eur. 8: (Spirapril Hydrochloride Monohydrate). A white or almost white, fine crystalline powder. Very slightly soluble in water; slightly soluble in acetonitrile; practically insoluble in dichloromethane; soluble in methyl alcohol. Store in airtight containers. Protect from light.

Profile

Spirapril is an ACE inhibitor (p. 1282.2) that is used in the management of hypertension (p. 1251.1). It owes its activity to the diacid spiraprilat, to which it is converted after oral doses. It is given orally as the hydrochloride in a usual maintenance dose of 6 mg once daily.

References.

1. Noble S, Sorkin EM. Spirapril: a preliminary review of its pharmacology and therapeutic efficacy in the treatment of hypertension. *Drugs* 1995; **49**: 750–66.
2. Widimský J, *et al.* Czech and Slovak spirapril intervention study (CASSIS): a randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur J Clin Pharmacol* 1995; **49**: 95–102.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Quadropril; *Cz.*: Renpress; *Ger.*: Quadropril; *Hung.*: Quadropril†; *Ital.*: Renormax; Setrilan; *Rus.*: Quadropril (Квадроприл); *Spain*: Renormax†; Renpress†; *Ukr.*: Quadropril (Квадроприл).

Spironolactone *(BAN, rINN)* ⊗

Espironolactona; SC-9420; Spirolactone; Spironolacton; Spironolactonum; Spironolakton; Spironolaktonas; Spironolaktoni; Спиронолактон.

7α-Acetylthio-3-oxo-17α-pregn-4-ene-21,17β-carbolactone; (7α,17α)-7-(Acetylthio)-17-hydroxy-3-oxo-pregn-4-ene-21-carboxylic acid γ-lactone.

$C_{24}H_{32}O_4S$=416.6.

CAS — 52-01-7.

ATC — C03DA01.

ATC Vet — QC03DA01
UNII — 27O7W4T232

NOTE. Compounded preparations of spironolactone may be represented by the following names:
- Co-flumactone (*BAN*)—spironolactone and hydroflumethiazide in equal parts (w/w)
- Co-spironozide (*PEN*)—spironolactone and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Spironolactone). A white or yellowish-white powder. Practically insoluble in water; soluble in alcohol. It exhibits polymorphism. Protect from light.

USP 36: (Spironolactone). A light cream-coloured to light tan, crystalline powder with a faint to mild mercaptan-like odour. Practically insoluble in water; soluble in alcohol and in ethyl acetate; freely soluble in chloroform and in benzene; slightly soluble in methyl alcohol and in fixed oils.

Stability. There was no appreciable loss of spironolactone from extemporaneously prepared suspensions of spironolactone, 2.5, 5 and 10 mg/mL, in a cherry syrup after storage for 2 weeks at 5 degrees or 30 degrees or at ambient room temperature under intense fluorescent light.[1] Degradation was less than 5% for samples stored for 4 weeks, but was more noticeable in suspensions with a higher initial concentration. There were no changes in colour or odour. Bacterial and fungal counts were well within acceptable limits after 4 weeks at 30 degrees.

1. Mathur LK, Wickman A. Stability of extemporaneously compounded spironolactone suspensions. *Am J Hosp Pharm* 1989; 46: 2040–2.

Uses and Administration

Spironolactone, a steroid with a structure resembling that of the natural adrenocortical hormone aldosterone, acts on the distal portion of the renal tubule as a competitive antagonist of aldosterone. It acts as a potassium-sparing diuretic, increasing sodium and water excretion and reducing potassium excretion.

Spironolactone is reported to have a relatively slow onset of action, requiring 2 or 3 days for maximum effect, and a similarly slow diminishment of action over 2 or 3 days on stopping.

Spironolactone is used in the management of heart failure, both to treat refractory oedema and in lower doses as an adjunct to standard therapy (see below). It is also used for refractory oedema associated with cirrhosis of the liver (with or without ascites, p. 1276.2), or the nephrotic syndrome, and in ascites associated with malignancy. It is frequently given with the thiazides, furosemide, or similar diuretics, where it adds to their natriuretic but diminishes their kaliuretic effects, hence conserving potassium in those at risk from hypokalaemia. Diuretic-induced hypokalaemia and its management, including the role of potassium-sparing diuretics, is discussed under Effects on the Electrolyte Balance in the Adverse Effects of Hydrochlorothiazide, p. 1404.2. It has been used in the treatment of essential hypertension (in lower doses than for oedema), but in the UK is no longer recommended for use in either essential hypertension or idiopathic oedema; doubts have been expressed over its safety during long-term administration.

Spironolactone is also used in the diagnosis and treatment of primary hyperaldosteronism (p. 1501.1).

Other conditions in which spironolactone has been tried on the basis of its anti-androgenic properties include hirsutism, particularly in the polycystic ovary syndrome.

In the treatment of **oedema**, spironolactone is usually given in an initial oral dose of 100 mg daily, subsequently adjusted as necessary; some patients may require doses of up to 400 mg daily. In hepatic cirrhosis with ascites and oedema, patients with a urinary sodium/potassium ratio greater than 1 may be given an initial dose of spironolactone 100 mg daily while patients with a ratio of less than 1 may be given initial doses of 200 to 400 mg daily.

Spironolactone is given in doses of 400 mg daily in the presumptive diagnosis of primary **hyperaldosteronism**; in doses of 100 to 400 mg daily for the pre-operative management of hyperaldosteronism; and in the lowest effective dosage for long-term maintenance therapy in the absence of surgery.

For doses in children, see below.

Potassium supplements should not be given with spironolactone.

References and reviews.

1. Skluth HA, Gums JG. Spironolactone: a re-examination. *DICP Ann Pharmacother* 1990; 24: 52–9.
2. Doggrell SA, Brown L. The spironolactone renaissance. *Expert Opin Invest Drugs* 2001; 10: 943–54.
3. Sica DA. Spironolactone: an old friend rediscovered. *J Clin Hypertens (Greenwich)* 2006; 8: 467–9.
4. Dorrance AM. Stroke therapy: is spironolactone the Holy Grail? *Endocrinology* 2008; 149: 3761–3.
5. de Souza F, *et al.* Efficacy of spironolactone therapy in patients with true resistant hypertension. *Hypertension* 2010; 55: 147–52.
6. Williams JS. Hypertension: spironolactone and resistant hypertension. *Nat Rev Endocrinol* 2010; 6: 248–50.

Administration in children. Spironolactone may be given to neonates, infants, and children for the treatment of heart failure, oedema, and ascites. The *BNFC* recommends the following oral doses, based on age:
- neonates: 1 to 2 mg/kg daily in 1 or 2 divided doses; up to 7 mg/kg daily may be given in resistant ascites
- 1 month to 12 years: 1 to 3 mg/kg daily in 1 or 2 divided doses; up to 9 mg/kg daily may be given in resistant ascites
- 12 to 18 years: 50 to 100 mg daily in 1 or 2 divided doses; up to 9 mg/kg (maximum 400 mg) daily may be given in resistant ascites

The *BNFC* also suggests that these doses may be given for the reduction of hypokalaemia induced by diuretics or amphotericin.

References.
1. Buck ML. Clinical experience with spironolactone in pediatrics. *Ann Pharmacother* 2005; 39: 823–8.

Acne. Spironolactone has been used for its anti-androgenic properties in some cases of acne (p. 1682.2) where standard therapy is unsuccessful. Beneficial responses to oral therapy have been reported in patients with acne from both open[1] and placebo-controlled[2,3] studies, although a systematic review[4] considered that there was insufficient evidence for its efficacy. Topical application has been tried[5,6] but response has been variable. It is possible that the vehicle may affect the response. In women, spironolactone may be useful when treatment with an oestrogen is contra-indicated.

1. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; 112: 124–5.
2. Goodfellow A, *et al.* Oral spironolactone improves acne vulgaris and reduces sebum excretion. *Br J Dermatol* 1984; 111: 209–14.
3. Muhlemann MF, *et al.* Oral spironolactone: an effective treatment for acne vulgaris in women. *Br J Dermatol* 1986; 115: 227–32.
4. Brown J, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 26/02/10).
5. Messina M, *et al.* A new therapeutic approach to acne: an antiandrogen percutaneous treatment with spironolactone. *Curr Ther Res* 1983; 34: 319–24.
6. Walton S, *et al.* Lack of effect of topical spironolactone on sebum excretion. *Br J Dermatol* 1986; 114: 261–4.

Alopecia. Anti-androgens have a role in the treatment of hirsutism (see below) but have also been used in patients with androgenetic alopecia (p. 1682.3), and there is some evidence that spironolactone may be effective.[1-3]

1. Sinclair R, *et al.* Treatment of female pattern hair loss with oral antiandrogens. *Br J Dermatol* 2005; 152: 466–73.
2. Hoedemaker C, *et al.* Treatment of female pattern hair loss with a combination of spironolactone and minoxidil. *Australas J Dermatol* 2007; 48: 43–5.
3. Yazdabadi A, *et al.* Successful treatment of female-pattern hair loss with spironolactone in a 9-year-old girl. *Australas J Dermatol* 2009; 50: 113–14.

Bartter's syndrome. Spironolactone may be used to reduce potassium wasting in patients with Bartter's syndrome (p. 1779.3).

Bronchopulmonary dysplasia. Bronchopulmonary dysplasia (p. 1602.1) is a major cause of chronic lung disease in infants. Treatment often involves the use of corticosteroids. Additional supportive therapy has included the use of diuretics such as furosemide (p. 1387.3); results with hydrochlorothiazide or spironolactone have been more ambiguous (p. 1403.3).

Heart failure. Drug therapy of heart failure (p. 1262.3) is based on the use of diuretics, ACE inhibitors, cardiac glycosides, beta blockers, and vasodilators. Spironolactone has been used as a diuretic for refractory oedema, but it also has an additional role as an aldosterone antagonist.[1,2] Although the precise neurohormonal mechanisms leading to the development of heart failure are still not clear, there is evidence that raised levels of aldosterone may contribute to the pathophysiology.[3,4] ACE inhibitor therapy suppresses aldosterone production but this effect is not complete and the use of spironolactone with ACE inhibitors has therefore been studied. In the Randomized Aldactone Evaluation Study (RALES)[5] in patients with severe heart failure, addition of spironolactone in a dose of 25 to 50 mg daily to therapy with ACE inhibitors and loop diuretics reduced the risk of death or hospitalisation.[5] The use of spironolactone may be considered in patients with moderate to severe heart failure.[6-9] The benefit may be a class effect: a systematic review[10] found a 20% reduction in all-cause mortality when spironolactone, eplerenone, or canrenone were given to patients with left-ventricular dysfunction or after myocardial infarction. A small study[11] has also shown benefit in patients with less milder heart failure. However, use of spironolactone with ACE inhibitors may lead to hyperkalaemia and careful monitoring of potassium concentrations is required[12,13] (see Interactions, p. 1502.2). Retrospective analyses[14,15] of heart failure patients found that some 10 to 15% had to stop spironolactone because of hyperkalaemia, and a similar proportion stopped because of worsening renal function. Risk factors were advanced age and higher baseline plasma-potassium concentrations.

1. Tang WHW, *et al.* Aldosterone receptor antagonists in the medical management of chronic heart failure. *Mayo Clin Proc* 2005; 80: 1623–30.
2. Marcy TR, Ripley TL. Aldosterone antagonists in the treatment of heart failure. *Am J Health-Syst Pharm* 2006; 63: 49–58.
3. Struthers AD. Why does spironolactone improve mortality over and above an ACE inhibitor in chronic heart failure? *Br J Clin Pharmacol* 1999; 47: 479–82.
4. Rocha R, Williams GH. Rationale for the use of aldosterone antagonists in congestive heart failure. *Drugs* 2002; 62: 723–31.
5. Pitt B, *et al.* The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709–17.
6. Jessup M, *et al.* 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009; 119: 1977–2016. Correction. *ibid.*; 121:e258. Also published in *J Am Coll Cardiol* 2009: 53: e1–e90. Correction. *ibid.*; 54: 2464 Also available at: http://circ.ahajournals.org/cgi/reprint/119/14/1977.pdf (accessed 11/10/10) and at: http://content.onlinejacc.org/cgi/reprint/53/15/e1.pdf (accessed 11/10/10)
7. Dickstein K, *et al.* Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur Heart J* 2008; 29: 2388–2442. Correction. *ibid.* 3069. [dose] Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf (accessed 14/10/08)
8. Scottish Intercollegiate Guidelines Network. Management of chronic heart failure (February 2007). Available at: http://www.sign.ac.uk/pdf/sign95.pdf (accessed 07/05/08)
9. NICE. Chronic heart failure: management of chronic heart failure in adults in primary and secondary care (issued August 2010). Available at: http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf (accessed 13/10/10)
10. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 2009; 30: 469–77.
11. Macdonald JE, *et al.* Effects of spironolactone on endothelial function, vascular angiotensin converting enzyme activity, and other prognostic markers in patients with mild heart failure already taking optimal treatment. *Heart* 2004; 90: 765–70.
12. Georges B, *et al.* Spironolactone and congestive heart-failure. *Lancet* 2000; 355: 1369–70.
13. Juurlink DN, *et al.* Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med* 2004; 351: 543–51.
14. Witham MD, *et al.* Tolerability of spironolactone in patients with chronic heart failure—a cautionary message. *Br J Clin Pharmacol* 2004; 58: 554–7.
15. Lopes RJ, *et al.* Safety of spironolactone use in ambulatory heart failure patients. *Clin Cardiol* 2008; 31: 509–13.

High-altitude disorders. Acetazolamide is generally the drug of choice for prophylaxis of high-altitude disorders (p. 1276.2). Anecdotal reports[1-4] and a small-scale double-blind study[5] suggested that spironolactone could be useful in preventing acute mountain sickness, although a deterioration in pulmonary function despite spironolactone prophylaxis has been noted in a patient.[6]

1. Currie TT, *et al.* Spironolactone and acute mountain sickness. *Med J Aust* 1976; 2: 168–70.
2. Snell JA, Cordner EP. Spironolactone and acute mountain sickness. *Med J Aust* 1977; 1: 828.
3. Turnbull G. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; 280: 1453.
4. Rutter LD. Spironolactone prophylaxis in mountain sickness. *BMJ* 1980; 281: 618.
5. Brown GV, *et al.* Spironolactone in acute mountain sickness. *Lancet* 1977; i: 855.
6. Meyers DH. Spironolactone prophylaxis of mountain sickness. *BMJ* 1980; 281: 1569.

Hirsutism. Hirsutism (p. 2262.1) is frequently treated with anti-androgens, usually cyproterone or spironolactone. Spironolactone in doses of 50 to 200 mg daily has produced both subjective and objective improvement in hirsutism in patients with idiopathic hirsutism or polycystic ovary syndrome,[1-4] and its use has been reviewed.[5] It is preferably used with oral contraceptives,[6,7] to improve efficacy and menstrual irregularity and to avoid the risk of feminisation to a male fetus. Most studies have involved premenopausal women and it has been suggested[4,8] that spironolactone would be useful in women in whom cyproterone is contra-indicated or not tolerated. A randomised study (not placebo-controlled) found spironolactone 100 mg daily and cyproterone 100 mg daily to be equally effective,[9] while a systematic review[10] of the use of spironolactone in hirsutism concluded that it was significantly more effective than both cyproterone and finasteride for up to 12 months after treatment.

For reference to the use of spironolactone in alopecia, see above.

1. Cumming DC, *et al.* Treatment of hirsutism with spironolactone. *JAMA* 1982; 247: 1295–8.
2. Burke BM, Cunliffe WJ. Oral spironolactone therapy for female patients with acne, hirsutism or androgenic alopecia. *Br J Dermatol* 1985; 112: 124–5.
3. Evans DJ, Burke CW. Spironolactone in the treatment of idiopathic hirsutism and the polycystic ovary syndrome. *J R Soc Med* 1986; 79: 451–3.

4. Barth JH, *et al.* Spironolactone therapy for hirsute women. *Br J Dermatol* 1988; 119 (suppl 33): 17.
5. Christy NA, *et al.* Spironolactone for hirsutism in polycystic ovary syndrome. *Ann Pharmacother* 2005; 39: 1517–21. Correction. *ibid.*; 1765.
6. Chapman MG, *et al.* Spironolactone in combination with an oral contraceptive: an alternative treatment for hirsutism. *Br J Obstet Gynaecol* 1985; 92: 983–5.
7. Rittmaster RS. Hirsutism. *Lancet* 1997; 349: 191–5.
8. West TBT. Does spironolactone have a place in treating facial hirsutism in women? *BMJ* 1988; 296: 1456.
9. O'Brien RC, *et al.* Comparison of sequential cyproterone acetate/estrogen versus spironolactone/oral contraceptive in the treatment of hirsutism. *J Clin Endocrinol Metab* 1991; 72: 1008–13.
10. Brown J, *et al.* Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 26/02/10).

Hyperaldosteronism. Hyperaldosteronism (aldosteronism) [1-6] is a disorder of mineralocorticoid excess characterised by high circulating levels of aldosterone. It is a common cause of secondary hypertension, and is frequently diagnosed in those with resistant hypertension. The cardiovascular risks associated with hyperaldosteronism are far greater than for those with primary hypertension,[7] therefore correct identification and treatment is important.

Hyperaldosteronism may be primary or secondary, the latter resulting from conditions in which there is activation of the renin-angiotensin-aldosterone system, including diuretic therapy, and oedematous conditions such as heart failure, hepatic cirrhosis, and nephrotic syndrome. Bartter's syndrome (p. 1779.3) also results in hyperaldosteronism. Primary hyperaldosteronism is less common, and is usually caused by either bilateral adrenal hyperplasia or unilateral aldosterone-producing adenoma (Conn's syndrome). Rarer causes of primary hyperaldosteronism include aldosterone-secreting adrenal carcinoma and familial forms such as glucocorticoid-remediable aldosteronism.

The classic presentation of hyperaldosteronism is of hypertension, hypokalaemia, and alkalosis, but most patients are normokalaemic, with symptomatic hypokalaemia present only in the most severe cases or in those taking diuretics. In general, those with severe or resistant hypertension, spontaneous or diuretic-induced hypokalaemia, or juvenile hypertension or stroke should be screened for primary hyperaldosteronism.[2,4] This is usually done by measuring the plasma aldosterone:renin ratio. In primary hyperaldosteronism the aldosterone concentration is raised but renin is suppressed, although this does not necessarily prove the **diagnosis**; in secondary hyperaldosteronism both are raised. The test may be confounded by circadian rhythm, posture, and drugs. Hypokalaemia should first be corrected, sodium intake increased, and spironolactone or eplerenone therapy stopped for at least 4 to 6 weeks beforehand. Antihypertensives that may be continued with a minimal effect on the aldosterone:renin ratio are the alpha-blockers and calcium-channel blockers. The diagnosis must be confirmed with suppression testing, either with volume expansion using sodium or fludrocortisone, or by blocking the renin-angiotensin-aldosterone system with an ACE inhibitor, usually captopril. Computed tomography imaging and adrenal vein sampling are used to identify adenoma from hyperplasia, and exclude carcinoma.

Unilateral laparoscopic adrenalectomy is the preferred **treatment** for unilateral adenoma,[1,3-6] improving hypertension and hypokalaemia in most patients although about half will need to continue antihypertensive therapy. An aldosterone antagonist such as spironolactone may be given pre-operatively to lower the blood pressure and normalise the serum potassium. In those not suitable for surgery, lifelong drug therapy is indicated. Bilateral hyperplasia is not surgically correctable and is also managed medically. There is most experience with spironolactone and it is the treatment of choice,[1,4,5] initially in high doses, reduced to the lowest effective dose for maintenance; eplerenone is an alternative if adverse effects are a problem. Amiloride has also been used, but high doses are required. A thiazide may be added to therapy to maximise the antihypertensive effect and minimise hyperkalaemia.[4]

Glucocorticoid-remediable hyperaldosteronism (GRA), also known as familial hyperaldosteronism type I (FH-I),[8] is a rare autosomal dominant form. It has been diagnosed using a dexamethasone-suppression test, but direct identification with genetic testing is now preferred. It is treated with a long-acting glucocorticoid such as dexamethasone or prednisone, with the addition of spironolactone, eplerenone, or amiloride if hypertension remains uncontrolled.

In secondary hyperaldosteronism the underlying condition should be treated, but diuretics such as spironolactone may be of benefit as part of the therapy.

1. Pimenta E, Calhoun DA. Primary aldosteronism: diagnosis and treatment. *J Clin Hypertens (Greenwich)* 2006; 8: 887–93.
2. Rossi GP, *et al.* Primary aldosteronism - part I: prevalence, screening, and selection of cases for adrenal vein sampling. *J Nephrol* 2008; 21: 447–54.
3. Rossi GP, *et al.* Primary aldosteronism: part II: subtype differentiation and treatment. *J Nephrol* 2008; 21: 455–62.
4. Funder JW, *et al.* Endocrine Society. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008; 93: 3266–81.
5. Carey RM. Primary aldosteronism. *Horm Res* 2009; 71 (suppl 1): 8–12.
6. Schirpenbach C, *et al.* The diagnosis and treatment of primary hyperaldosteronism in Germany: results on 555 patients from the German Conn Registry. *Dtsch Arztebl Int* 2009; 106: 305–11.
7. Catena C, *et al.* Cardiovascular outcomes in patients with primary aldosteronism after treatment. *Arch Intern Med* 2008; 168: 80–5.
8. McMahon GT, Diuhy RG. Glucocorticoid-remediable aldosteronism. *Arq Bras Endocrinol Metabol* 2004; 48: 682–6.

Kidney disorders. There is evidence that aldosterone may play a role in the development of chronic kidney disease; although patients must be carefully monitored because of the risk of hyperkalaemia (see also Precautions, p. 1502.1) low-dose spironolactone has been investigated for its potential as an adjunct to reduce proteinuria and potentially retard the development of renal impairment in both diabetic and non-diabetic patients.[1-4]

1. Furumatsu Y, *et al.* Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease: addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. *Hypertens Res* 2008; 31: 59–67.
2. Saklayen MG, *et al.* Effects of additive therapy with spironolactone on proteinuria in diabetic patients already on ACE inhibitor or ARB therapy: results of a randomized, placebo-controlled, double-blind, crossover trial. *J Investig Med* 2008; 56: 714–19.
3. Sengul E, *et al.* Effect of spironolactone on urinary protein excretion in patients with chronic kidney disease. *Ren Fail* 2009; 31: 928–32.
4. Bomback AS, *et al.* Renal aspirin: will all patients with chronic kidney disease one day take spironolactone? *Nat Clin Pract Nephrol* 2009; 5: 74–5.

Precocious puberty. Spironolactone (as an anti-androgen) and testolactone were given to boys with familial precocious puberty (p. 2254.1) for periods of up to 18 months. Rates of growth and bone maturation were restored to normal during combination therapy but not with either drug given alone.[1] However, after further treatment for 2 to 4.2 years there was a diminishing response manifested by the recurrence of clinical features of puberty and an increase in the bone maturation rate.[2] Addition of deslorelin appeared to restore the control of puberty,[2] and in a long-term study[3] growth rate remained normal for 6 years.

1. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone and testolactone. *N Engl J Med* 1989; 320: 496–502.
2. Laue L, *et al.* Treatment of familial male precocious puberty with spironolactone, testolactone, and deslorelin. *J Clin Endocrinol Metab* 1993; 76: 151–5.
3. Leschek EW, *et al.* Six-year results of spironolactone and testolactone treatment of familial male-limited precocious puberty with addition of deslorelin after central puberty onset. *J Clin Endocrinol Metab* 1999; 84: 175–8.

Premenstrual syndrome. Spironolactone has been used for its diuretic and anti-androgenic properties in premenstrual syndrome (p. 2272.3).

Adverse Effects

Spironolactone may give rise to headache and drowsiness, and gastrointestinal disturbances, including cramp and diarrhoea. Ataxia, mental confusion, and rashes have been reported as adverse effects. Gynaecomastia is not uncommon and in rare cases breast enlargement may persist. Other endocrine disorders include hirsutism, deepening of the voice, menstrual irregularities, and impotence. Transient increases in blood-urea-nitrogen concentrations may occur and mild acidosis has been reported. Spironolactone has been shown to cause tumours in *rats*.

Spironolactone may cause hyponatraemia and hyperkalaemia.

Incidence of adverse effects. A survey found that of 788 patients given spironolactone 164 developed adverse effects.[1] These included hyperkalaemia in 8.6%, dehydration in 3.4%, hyponatraemia in 2.4%, gastrointestinal disorders in 2.3%, neurological disorders in 2%, rash, and gynaecomastia. Hyperkalaemia was associated with renal impairment and the use of potassium supplements: only 2.8% of nonuraemic patients not receiving potassium chloride developed hyperkalaemia, while 42.1% of those with marked uraemia and treated with potassium chloride became hyperkalaemic.

In a study[2] of 54 patients (53 female, 1 male) taking spironolactone 200 mg daily for hirsutism or acne adverse effects were reported in 91%.[2] Menstrual disturbances occurred in 72% of patients, breast tenderness in 39%, dry skin in 39%, and breast enlargement in 24%. Other adverse effects included nausea and vomiting, dizziness, headache, drowsiness, and rashes. Two patients developed a chloasma-like pigmentation of the face. The gynaecological effects were reduced in patients taking oral contraceptives.

1. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; 225: 40–3.
2. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; 118: 687–91.

Carcinogenicity. Breast cancer was reported in 5 patients taking spironolactone and hydrochlorothiazide for prolonged periods[1] although it was suggested[2] that the association with spironolactone therapy was unlikely to be causal.

Although the *rat* may not be an appropriate model for determining long-term safety in man,[3,4] evidence of carcinogenicity in this species prompted the UK CSM to limit the product licences of spironolactone-containing products to exclude use in essential hypertension or idiopathic oedema.[5]

1. Loube SD, Quirk RA. Breast cancer associated with administration of spironolactone. *Lancet* 1975; i: 1428–9.
2. Jick H, Armstrong B. Breast cancer and spironolactone. *Lancet* 1975; ii: 368–9.
3. Lumb G, *et al.* Effects in animals of chronic administration of spironolactone—a review. *J Environ Pathol Toxicol* 1978; 1: 641–60.
4. Wagner BM. Long-term toxicology studies of spironolactone in animals and comparison with potassium canrenoate. *J Drug Dev* 1987; 1 (suppl 2): 7–11.
5. CSM. Spironolactone. *Current Problems* 1988; 21. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024428&RevisionSelectionMethod=LatestReleased (accessed 25/07/08)

Effects on the blood. Agranulocytosis has been reported[1,2] in association with the use of spironolactone.

1. Stricker BHC, Oei TT. Agranulocytosis caused by spironolactone. *BMJ* 1984; 289: 731.
2. Whitling AM, *et al.* Spironolactone-induced agranulocytosis. *Ann Pharmacother* 1997; 31: 582–5.

Effects on electrolyte balance. *CALCIUM.* A report[1] suggested that spironolactone may have a calcium-sparing effect, in addition to its well known potassium-sparing properties.

1. Puig JG, *et al.* Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J Clin Pharmacol* 1991; 31: 455–61.

POTASSIUM. There have been reports[1-3] of severe hyperkalaemia in patients taking spironolactone, including patients with renal impairment and those with a high potassium intake from either dietary sources or potassium supplements. In the Boston Collaborative Drug Surveillance Program[4] hyperkalaemia was reported in 42.1% of patients with uraemia taking spironolactone and receiving potassium supplements compared with 2.8% of those without uraemia and not receiving potassium supplements. Two deaths were attributed to hyperkalaemia in patients taking spironolactone and potassium chloride. Potassium supplements should be avoided in patients receiving spironolactone, and plasma-potassium concentrations should be carefully monitored in those with renal impairment. An analysis[5] of spironolactone prescriptions in a Scottish population between 1994 and 2007, however, noted that despite an increase in prescription after 1999 following the results of the RALES study, there was no concomitant increase in hospital admissions for hyperkalaemia, and instances of measured hyperkalaemia in outpatients actually fell, suggesting that careful monitoring enabled successful use of the drug.

1. Pongpaew C, *et al.* Hyperkalemic cardiac arrhythmia secondary to spironolactone. *Chest* 1973; 63: 1023–5.
2. Udezue EO, Harrold BP. Hyperkalaemic paralysis due to spironolactone. *Postgrad Med J* 1980; 56: 254–5.
3. O'Reilly PH, *et al.* Life-threatening hyperkalaemia after bladder decompression for high pressure chronic retention. *Lancet* 1987; ii: 859.
4. Greenblatt DJ, Koch-Weser J. Adverse reactions to spironolactone: a report from the Boston Collaborative Drug Surveillance Program. *JAMA* 1973; 225: 40–3.
5. Wei L, *et al.* Spironolactone use and renal toxicity: population based longitudinal analysis. *BMJ* 2010; 340: c1768.

Effects on endocrine function. Spironolactone has been associated with disturbances of endocrine function. The most prominent in men is gynaecomastia which appears to be related to both dose and duration of treatment. Incidences of 62%[1] and 100%[2] have been reported. Gynaecomastia has also been accompanied by impotence.[3,4] The effects are generally reversible on stopping treatment. Reversal of male-pattern baldness has also been reported.[5]

In women symptoms include breast enlargement and tenderness.[6] The incidence of menstrual abnormalities may be high: unspecified disturbances have been reported in 33 of 53 women,[6] secondary amenorrhoea in 6 of 9,[7] and secondary and primary amenorrhoea in 1 and 2 patients, respectively.[8] The incidence of gynaecological disturbances has been found to be lower in women taking oral contraceptives.[6]

The mechanism of the effects of spironolactone on the endocrine system is unclear. Some workers[9] suggested that although spironolactone affects testosterone synthesis, the more likely explanation was its anti-androgenic action, and reduction in 17-hydroxylase activity. Others[10] found an alteration in the testosterone/oestrogen ratio due to an increase in testosterone clearance and increased peripheral conversion to estradiol. In addition, spironolactone is reported to inhibit binding of dihydrotestosterone to receptors.

1. Huffman DH, *et al.* Gynecomastia induced in normal males by spironolactone. *Clin Pharmacol Ther* 1978; 24: 465–73.

2. Bellati G, Idéo G. Gynaecomastia after spironolactone and potassium canrenoate. *Lancet* 1986; **i**: 626.
3. Greenblatt DJ, Koch-Weser J. Gynecomastia and impotence complications of spironolactone therapy. *JAMA* 1973; **223**: 82.
4. Greenlaw C. Spironolactone induced gynecomastia: a case report. *Drug Intell Clin Pharm* 1977; **11**: 70–3.
5. Thomas PS. Hair: wanted and unwanted. *BMJ* 1986; **293**: 698.
6. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118**: 687–91.
7. Levitt JL. Spironolactone therapy and amenorrhea. *JAMA* 1970; **211**: 2014–15.
8. Potter C, *et al.* Primary and secondary amenorrhea associated with spironolactone therapy in chronic liver disease. *J Pediatr* 1992; **121**: 141–3.
9. Loriaux DL, *et al.* Spironolactone and endocrine dysfunction. *Ann Intern Med* 1976; **85**: 630–6.
10. Rose LI, *et al.* Pathophysiology of spironolactone-induced gynecomastia. *Ann Intern Med* 1977; **87**: 398–403.

Effects on the gastrointestinal tract. Population-based studies[1-3] have identified a dose-dependent increased risk of gastrointestinal bleeding and ulcers in those taking spironolactone. The mechanism was thought to be inhibition of aldosterone-induced formation of fibrous tissue, thus impairing the healing of gastric and duodenal erosion.

1. Verhamme KMC, *et al.* Spironolactone and risk of upper gastrointestinal events: population based case-control study. Abridged version: *BMJ* 2006; **333**: 330–333. Full version: http://www.bmj.com/cgi/reprint/333/7563/330.pdf (accessed 20/05/10)
2. Russo A, *et al.* Spironolactone and gastrointestinal bleeding: a population based study. *Pharmacoepidemiol Drug Safety* 2008; **17**: 495–500.
3. Gulmez SE, *et al.* Spironolactone use and the risk of upper gastrointestinal bleeding: a population-based case-control study. *Br J Clin Pharmacol* 2008; **66**: 294–9.

Effects on lipid metabolism. Unlike thiazide diuretics, spironolactone appeared not to increase serum-cholesterol concentrations in a study of 23 patients.[1]

1. Ames RP, Peacock PB. Serum cholesterol during treatment of hypertension with diuretic drugs. *Arch Intern Med* 1984; **144**: 710–14.

Effects on the liver. Hepatotoxicity characterised by cholestatic lesions has been reported in a patient receiving spironolactone.[1] Only one other published case of spironolactone-associated hepatotoxicity was known to the authors.

1. Renkes P, *et al.* Spironolactone and hepatic toxicity. *JAMA* 1995; **273**: 376–7.

Effects on the skin. Lichen-planus-like skin eruptions developed in a 62-year-old woman who was taking digoxin, propranolol, diazepam, spironolactone, and iron tablets.[1] Flares of the lichen-planus-like eruption seemed to be associated with use of spironolactone and there was evidence of resolution when spironolactone was withdrawn. Cutaneous vasculitis was associated with spironolactone on 3 occasions in an 80-year-old man.[2] A chloasma-like pigmentation of the face was reported in 2 patients receiving spironolactone for hirsutism or acne.[3]

1. Downham TF. Spironolactone-induced lichen planus. *JAMA* 1978; **240**: 1138.
2. Phillips GWL, Williams AJ. Spironolactone induced vasculitis. *BMJ* 1984; **288**: 368.
3. Hughes BR, Cunliffe WJ. Tolerance of spironolactone. *Br J Dermatol* 1988; **118**: 687–91.

Hypersensitivity. Eosinophilia and a rash developed in 2 patients with alcoholic cirrhosis while taking spironolactone.[1] A report of the DRESS syndrome (drug rash with eosinophilia and systemic symptoms) has also been associated[2] with spironolactone.

1. Wathen CG, *et al.* Eosinophilia associated with spironolactone. *Lancet* 1986; **i**: 919–20.
2. Ghislain PD, *et al.* Drug-induced eosinophilia and multisystemic failure with positive patch-test reaction to spironolactone: DRESS syndrome. *Acta Derm Venereol* 2004; **84**: 65–8.

Precautions

Spironolactone should not be used in patients with hyperkalaemia or severe renal impairment. It should be used with care in patients who are at increased risk of developing hyperkalaemia; such patients include the elderly, those with diabetes mellitus, and those with some degree of renal or hepatic impairment. It should also be given with care to patients likely to develop acidosis. Serum electrolytes and blood-urea-nitrogen should be measured periodically.

Breast feeding. The concentration of canrenone was measured[1] in the serum and milk of a breast-feeding woman taking 25 mg of spironolactone four times daily. The milk to serum concentration ratios of canrenone at 2 and 14.5 hours after a dose of spironolactone were 0.72 and 0.51 respectively, and it was estimated that the amount of canrenone ingested by the infant would be 0.2% of the mother's daily dose of spironolactone. The serum potassium and sodium levels of the infant were in the normal range. The American Academy of Pediatrics[2] considers that spironolactone is therefore usually compatible with breast feeding.

1. Phelps DL, Karim A. Spironolactone: relationship between concentrations of dethioacetylated metabolite in human serum and milk. *J Pharm Sci* 1977; **66**: 1203.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *Ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Diabetes mellitus. Severe hyperkalaemia was reported in a type 1 diabetic woman with hyporeninaemic hypoaldosteronism given spironolactone.[1]

1. Large DM, *et al.* Hyperkalaemia in diabetes mellitus—potential hazards of coexisting hyporeninaemic hypoaldosteronism. *Postgrad Med J* 1984; **60**: 370–3.

Interference with laboratory estimations. Spironolactone and canrenoate can interfere with some assays for plasma-digoxin concentrations.[1-3] However, spironolactone may also produce actual changes in digoxin concentrations (see p. 1357.2) and results of assays should be interpreted with caution.

1. Josselson-Superstine S. Drug interferences with plasma assays in therapeutic drug monitoring. *Clin Pharmacokinet* 1984; **9**: 67–87.
2. Foukaridis GN. Influence of spironolactone and its metabolite canrenone on serum digoxin assays. *Ther Drug Monit* 1990; **12**: 82–4.
3. Stelmer W, *et al.* Intoxication due to negative canrenone interference in digoxin drug monitoring. *Lancet* 1999; **354**: 1176–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies spironolactone as porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be taken in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

There is an increased risk of hyperkalaemia if spironolactone is given with potassium supplements or with other potassium-sparing diuretics. Hyperkalaemia may occur as well in patients also given ACE inhibitors, angiotensin II receptor antagonists, NSAIDs, ciclosporin, or trilostane. In patients given spironolactone with NSAIDs or ciclosporin the risk of nephrotoxicity may also be increased. Diuretics may reduce the excretion of lithium and increase the risk of lithium toxicity. Hyponatraemia may occur in patients taking a potassium-sparing diuretic with a thiazide; this risk may be increased in patients given chlorpropamide. Spironolactone may reduce the ulcer-healing properties of carbenoxolone. As with other diuretics, spironolactone may enhance the effects of other antihypertensive drugs and may reduce vascular responses to noradrenaline.

ACE inhibitors and angiotensin II receptor antagonists. Severe hyperkalaemia has been reported in patients given spironolactone with ACE inhibitors or angiotensin II receptor antagonists and fatalities have occurred. In a study[1] of 44 patients taking such combinations for heart failure who were admitted to hospital with life-threatening hyperkalaemia, 37 required haemodialysis and 2 developed fatal complications. In another group[2] of 25 patients given spironolactone with ACE inhibitors who were admitted with severe hyperkalaemia, 2 died and 4 others developed severe cardiac arrhythmias. Advanced age, renal impairment or diabetes mellitus were risk factors for hyperkalaemia in both studies. It was suggested that combinations of spironolactone with ACE inhibitors or angiotensin II receptor antagonists should be used with caution in such patients and that they should not be given doses of spironolactone above 25 mg daily.

1. Wrenger E, *et al.* Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. *BMJ* 2003; **327**: 147–9.
2. Schepkens H, *et al.* Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. *Am J Med* 2001; **110**: 438–41.

Aspirin. Aspirin has been shown to produce substantial reductions in sodium excretion[1] in healthy subjects taking spironolactone and to reduce the excretion of spironolactone's active metabolite, canrenone.[2] However, use of aspirin in hypertensive patients[3] did not alter the effect of spironolactone on blood pressure, serum electrolytes, blood urea nitrogen, or plasma-renin activity.

1. Tweeddale MG, Ogilvie RI. Antagonism of spironolactone-induced natriuresis by aspirin in man. *N Engl J Med* 1973; **289**: 198–200.
2. Ramsay LE, *et al.* Influence of acetylsalicylic acid on the renal handling of a spironolactone metabolite in healthy subjects. *Eur J Clin Pharmacol* 1976; **10**: 43–8.
3. Hollifield JW. Failure of aspirin to antagonize the antihypertensive effect of spironolactone in low-renin hypertension. *South Med J* 1976; **69**: 1034–6.

Cardiac glycosides. For discussions of the effects of spironolactone on *digoxin* and *digitoxin*, see p. 1357.2 and p. 1353.3, respectively. See also Interference with Laboratory Estimations, under Precautions, above.

Mitotane. For a report of the inhibition of the action of mitotane by spironolactone, see p. 833.1.

Warfarin. For reference to the interaction between warfarin and spironolactone, see p. 1533.3.

Pharmacokinetics

Spironolactone is well absorbed from the gastrointestinal tract, with a bioavailability of about 90%. It is about 90% bound to plasma proteins.

Spironolactone is metabolised extensively to several metabolites including canrenone and 7α-thiomethylspirolactone, both of which are pharmacologically active. The major metabolite may be 7α-thiomethylspirolactone, although it is uncertain to what extent the actions of spironolactone are dependent on the parent compound or its metabolites.

Spironolactone is excreted mainly in the urine and also in the faeces, in the form of metabolites. Spironolactone or its metabolites may cross the placental barrier, and canrenone is distributed into breast milk.

References.

1. Overdiek HWPM, Merkus FWHM. The metabolism and biopharmaceutics of spironolactone in man. *Rev Drug Metab Drug Interact* 1987; **5**: 273–302.
2. Gardiner P, *et al.* Spironolactone metabolism: steady-state serum levels of the sulfur-containing metabolites. *J Clin Pharmacol* 1989; **29**: 342–7.
3. Sungaila I, *et al.* Spironolactone pharmacokinetics and pharmacodynamics in patients with cirrhotic ascites. *Gastroenterology* 1992; **102**: 1680–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aldactone; Drimux A; Espimax; Expal; Lanx; Modulactone; Normital; Osiren; Rediun-E; *Austral.*: Aldactone; Spiractin; *Austria*: Aldactone; Spirobene; Spirohexal; Spirono; *Belg.*: Aldactone; Docspironot†; Spirotop†; *Braz.*: Aldactone; Diacqua; Espirolona; Spiroctan; *Canad.*: Aldactone; Novo-Spiroton†; *Chile*: Alizar; Cardactona; *China*: Shi Er Tong (使尔通); Cz.: Verospiron; *Denm.*: Hexalacton; Spirix; Spiron; *Fin.*: Spiresist†; Spirix; *Fr.*: Aldactone; Flumach†; Practon†; Spiroctan; Spirononet†; *Ger.*: Aldactone; Jenaspiron; Osyrol†; Spiro; Spirobeta; Spirogamma; Spirono†; Verospiron; *Gr.*: Aldactone; Rocanol; Spinoral; Uridactone; *Hong Kong*: Aldactone; Spiractin†; *Hung.*: Huma-Spiroton; Spiron; Verospiron; *India*: Aldactone; *Indon.*: Aldactone; Carpiaton; Letonal; Spirola; Spirolacton; *Irl.*: Aldactone; *Israel*: Aldactone; Aldospiront; Spironol; *Ital.*: Aldactone; Spirolang; Uractone; *Malaysia*: Spirolon; *Mex.*: Aldactone; Biolactona; Nolasque; Vivitar; *Norw.*: Aldactone; Spirix; *NZ*: Spirotone; *Philipp.*: Aldactone; *Pol.*: Spironol; Verospiron; *Port.*: Aldactone; Aldonart; *Rus.*: Verospilactone (Верошпилактон); Verospiron (Верошпирон); *S. Afr.*: Aldactone; Spiractin; *Singapore*: Aldactone; Spirolon; Uractonum; *Spain*: Aldactone; *Swed.*: Aldactone; *Switz.*: Aldactone; Primacton†; Xenalon; *Thai.*: Aldactone; Altone; Hyles; Pondactone; Spironex; *Turk.*: Aldactone; *UK*: Aldactone; *Ukr.*: Verospiron (Верошпирон); *USA*: Aldactone; *Venez.*: Aldactone.

Multi-ingredient Preparations. *Arg.*: Aldactone HCT; Aldactone-D; Aldazida; Lasilacton; *Austria*: Aldactone Saltucin; Furo-Spirobene; Lasilacton; Sali-Aldopur; Spirono comp; *Belg.*: Aldactazine; Docspirochlor†; *Braz.*: Aldazida; Lasilactona; *Canad.*: Aldactazide; Apo-Spirozide†; Novo-Spirozine†; *Fr.*: Aldactazine; Aldalix; Practazin†; Spiroctazine; *Ger.*: Furo-Aldopur†; Furorese Comp†; Osyrol Lasix†; Spiro comp; Spiro-D†; Spironothiazid; *Gr.*: Aldactazide; Aldactazine; *India*: Aldactide; Aldostix; Amifru-S; Aquamide; Dyamide Plus; Dytor Plus; Fruselac; Lasilactone; Minilactone; Spiromide; *Indon.*: Aldazide; *Irl.*: Aldactide†; *Ital.*: Aldactazide; Lasitone; Spiridazide; Spirofur; *Mex.*: Aldazida; Lasilacton; *Philipp.*: Aldazide; *Port.*: Aldactazine; Ondolen; *S.Afr.*: Aldazide; *Spain*: Aldactacine; Aldoleo; *Switz.*: Aldozone†; Furospir; Lasilactone; *Turk.*: Aldactazide; *UK*: Aldactide; Lasilactone; *USA*: Aldactazide; *Venez.*: Aldactazida.

Pharmacopoeial Preparations

BP 2014: Spironolactone Oral Suspension; Spironolactone Tablets;

USP 36: Spironolactone and Hydrochlorothiazide Oral Suspension; Spironolactone and Hydrochlorothiazide Tablets; Spironolactone Oral Suspension; Spironolactone Tablets.

Staphylokinase

Estafilocinasa; Estafilokinasa; Estafiloquinasa; Staphylokinasa.

Profile

Staphylokinase is a thrombolytic derived from *Staphylococcus aureus*. Recombinant and modified forms are under investigation for the treatment of thromboembolic disorders, including acute myocardial infarction.

References.
1. Vanderschueren S, *et al.* Thrombolytic therapy of peripheral arterial occlusion with recombinant staphylokinase. *Circulation* 1995; 92: 2050–57.
2. Vanderschueren S, *et al.* Randomized coronary patency trial of double-bolus recombinant staphylokinase versus front-loaded alteplase in acute myocardial infarction. *Am Heart J* 1997; 134: 213–19.
3. Armstrong PW, *et al.* Collaborative angiographic patency trial of recombinant staphylokinase (CAPTORS II). *Am Heart J* 2003; 146: 484–8.
4. Verhamme P, *et al.* A dose-finding clinical trial of staphylokinase SY162 in patients with long-term venous access catheter thrombotic occlusion. *J Thromb Thrombolysis* 2007; 24: 1–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Shi Ai Ke (施爱克); Yi Li Tong (依力通).

Streptokinase *(BAN, rINN)*

Estreptokinasa; Estreptoquinasa; Plasminokinase; Sterptokinasum; Streptokinaasi; Streptokinas; Streptokinasum; Sztreptokináz; Стрептокиназа.

CAS — 9002-01-1.
ATC — B01AD01.
ATC Vet — QB01AD01.
UNII — 8X1OXL3SNU.

Pharmacopoeias. *Eur.* (see p. vii) includes a concentrated solution.

Ph. Eur. 8: (Streptokinase Concentrated Solution; Streptokinasi Solutio Concentrata). A preparation of a protein obtained from culture filtrates of certain strains of haemolytic *Streptococcus* group C. It has the property of combining with human plasminogen to form plasminogen activator. The potency is not less than 510 international units per microgram of nitrogen. A clear, colourless liquid. pH 6.8 to 7.5. Store in airtight containers at a temperature of -20 degrees. Protect from light.

Stability. The incorporation of albumin in commercial preparations of streptokinase has reduced the incidence of flocculation with streptokinase solutions. However, flocculation has occurred with small volumes prepared with sodium chloride 0.9% in sterilised glass containers apparently because of residual acid buffers that remain in empty evacuated containers after sterilisation.[1]

1. Thibault L. Streptokinase flocculation in evacuated glass bottles. *Am J Hosp Pharm* 1985; 42: 278.

Units

The potency of streptokinase is expressed in international units and preparations are assayed using the third International Standard (2001).

The Christensen unit is the quantity of streptokinase that will lyse a standard blood clot completely in 10 minutes and is equivalent to the international unit.

Uses and Administration

Streptokinase is a thrombolytic drug derived from various streptococci. It rapidly converts endogenous plasminogen, indirectly by means of a streptokinase-plasminogen complex, to its active form plasmin (see Fibrinolysin, p. 1382.3), resulting in fibrinolysis and dissolution of clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Streptokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p. 1245.3).

Streptokinase is given by intravenous or sometimes intra-arterial infusion in the treatment of thromboembolic disorders such as myocardial infarction (p. 1257.1), peripheral arterial thromboembolism (p. 1504.1), and venous thromboembolism (deep-vein thrombosis and pulmonary embolism) (p. 1274.1). It has also been tried in ischaemic stroke (p. 1504.2), although alteplase is generally preferred. Streptokinase may be used to clear cannulas and shunts and is used topically with streptodornase to clear clots and purulent matter.

In acute **myocardial infarction** streptokinase is usually given intravenously as a single dose of 1.5 million units infused over 1 hour as soon as possible after the onset of symptoms. Streptokinase has also been given in a suitable dose by intracoronary infusion but coronary catheterisation with the aid of angiography is required, thus restricting use to suitably equipped centres.

In the treatment of **pulmonary embolism** and other **arteriovenous occlusions** an initial loading dose of streptokinase, normally 250 000 units infused intravenously over 30 minutes, is given to overcome any resistance due to circulating antibodies. This is followed by infusion of a maintenance dose of 100 000 units/hour for 24 to 72 hours, depending on the condition to be treated; for central retinal thrombosis, 12 hours may be adequate. Treatment should be controlled by monitoring the thrombin clotting time, which should be maintained at 2 to 4 times normal values. Since thrombolytic activity rapidly fades when the infusion stops, streptokinase treatment is generally followed after 3 to 4 hours by intravenous heparin infusion, and then oral anticoagulation, to prevent re-occlusion.

Streptokinase, as a solution containing 250 000 units in 2 mL is used to clear occluded **cannulas**.

For doses in children, see below.

General references.
1. Pears R. Biochemical pharmacology and therapeutic aspects of thrombolytic agents. *Pharmacol Rev* 1990; 42: 201–21.
2. Stringer KA. Beyond thrombolysis: other effects of thrombolytic drugs. *Ann Pharmacother* 1994; 28: 752–6.
3. Ludlam CA, *et al.* Guidelines for the use of thrombolytic therapy. *Blood Coag Fibrinol* 1995; 6: 273–85.
4. Bell WR. Present-day thrombolytic therapy: therapeutic agents—pharmacokinetics and pharmacodynamics. *Rev Cardiovasc Med* 2002; 3 (suppl 2): S34–S44.

Administration in children. There are limited data on the use of systemic thrombolytic therapy for arterial or venous thromboembolism in children and various dosage regimens have been used, based on case studies. The most widely used drugs are streptokinase and alteplase. For streptokinase, the Eighth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy[1] suggests a loading dose of 2000 units/kg to be given intravenously, followed by continuous infusion of 2000 units/kg per hour for 6 to 12 hours. In the UK, for children aged from 1 month to 12 years, the *BNFC* suggests a loading dose of 2500 to 4000 units/kg over 30 minutes, followed by infusion of 500 to 1000 units/kg per hour, continued until reperfusion occurs, up to a maximum of 3 days. Children aged 12 years and over may be given the usual adult dose (see above).

Alteplase may be preferred because of its fibrin specificity and low immunogenicity. The dose of alteplase suggested by the ACCP is 100 to 600 micrograms/kg per hour by continuous intravenous infusion over 6 hours. In the UK, for neonates and children up to 18 years of age, the dose recommended by the *BNFC* is 100 to 500 micrograms/kg per hour for 3 to 6 hours (maximum total daily dose of 100 mg). The use of alteplase to clear occluded catheters in children is discussed on p. 1297.2.

1. Monagle P, *et al.* Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 887S–968S. Also available at: http://chestjournal.chestpubs.org/content/133/6_suppl/887S.full.pdf (accessed 23/10/09)

Empyema and pleural effusion. Thoracic empyema is treated with antibacterials and pleural drainage. Efficient removal of fluid may be impaired by fibrinous clots within the pleural cavity. Intrapleural instillation of streptokinase (100 000 to 750 000 units in up to 100 mL of sodium chloride 0.9%) has been reported to be effective in small series of patients[1–4] and there have been reports of the successful use of alteplase[5–7] and urokinase.[4,8] However, a double-blind study[9] involving 454 patients found no benefit with streptokinase, and the role of thrombolytics remains unclear. A meta-analysis[10] found no evidence of benefit, although a systematic review[11] suggested that thrombolytics may reduce the need for surgical intervention. Intrapleural streptokinase has also been used successfully in a few patients with malignant multiloculated pleural effusion resistant to standard pleural drainage.[12]

Intrapericardial instillation of thrombolytics has been tried in a few patients with pericardial empyema to prevent the development of constrictive pericarditis.[13,14]

For reports of haemorrhage associated with intrapleural use of streptokinase, see Haemorrhage, under Adverse Effects, p. 1505.3.

1. Temes RT, *et al.* Intrapleural fibrinolytics in management of empyema thoracis. *Chest* 1996; 110: 102–6.
2. Bouros D, *et al.* Role of streptokinase in the treatment of acute loculated parapneumonic pleural effusions and empyema. *Thorax* 1994; 49: 852–5.
3. Davies RJO, *et al.* Randomised controlled trial of intrapleural streptokinase in community acquired pleural infection. *Thorax* 1997; 52: 416–21.
4. Bouros D, *et al.* Intrapleural streptokinase versus urokinase in the treatment of complicated parapneumonic effusions: a prospective, double-blind study. *Am J Respir Crit Care Med* 1997; 155: 291–5.
5. Bishop NB, *et al.* Alteplase in the treatment of complicated parapneumonic effusion: a case report. Abstract: *Pediatrics* 2003; 111: 423. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/2/e188 (accessed 16/06/04)
6. Walker CA, *et al.* Intrapleural alteplase in a patient with complicated pleural effusion. *Ann Pharmacother* 2003; 37: 376–9.
7. Weinstein M, *et al.* Effectiveness and safety of tissue plasminogen activator in the management of complicated parapneumonic effusions. Abstract: *Pediatrics* 2004; 113: 610. Full version: http://pediatrics.aappublications.org/cgi/reprint/113/3/e182 (accessed 30/04/08)
8. Thomson AH, *et al.* Randomised trial of intrapleural urokinase in the treatment of childhood empyema. *Thorax* 2002; 57: 343–7.
9. Maskell NA, *et al.* U.K. controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med* 2005; 352: 865–74. Correction. *ibid.*; 2146.
10. Tokuda Y, *et al.* Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. *Chest* 2006; 129: 783–90.
11. Cameron RJ, Davies HRHR. Intra-pleural fibrinolytic therapy versus conservative management in the treatment of adult parapneumonic effusions and empyema. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 30/04/08).
12. Davies CWH, *et al.* Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. *Chest* 1999; 115: 729–33.
13. Winkler W-B, *et al.* Treatment of exudative fibrinous pericarditis with intrapericardial urokinase. *Lancet* 1994; 344: 1541–2.
14. Juneja R, *et al.* Intrapericardial streptokinase in purulent pericarditis. *Arch Dis Child* 1999; 80: 275–7.

Intracardiac thrombosis. Thrombosis of prosthetic heart valves (see p. 1264.3) is usually treated surgically, but thrombolytics have also been used. In a study[1] of patients with left-sided prosthetic valve thrombosis, thrombolytic therapy was found to be more successful than surgery, especially in those who were critically ill; most patients were given streptokinase. Another retrospective study[2] in which patients were given streptokinase, urokinase, or alteplase, concluded that thrombolytics were effective but embolic and haemorrhagic complications might limit their use. Treatment with tenecteplase[3] has successfully resolved intracardiac thrombosis in a patient implanted with a ventricular assist device.

1. Lengyel M, Vándor L. The role of thrombolysis in the management of left-sided prosthetic valve thrombosis: a study of 85 cases diagnosed by transesophageal echocardiography. *J Heart Valve Dis* 2001; 10: 636–49.
2. Roudaut R, *et al.* Fibrinolysis of mechanical prosthetic valve thrombosis: a single-center study of 127 cases. *J Am Coll Cardiol* 2003; 41: 653–8.
3. Hayes H, *et al.* Successful treatment of ventricular assist device associated ventricular thrombus with systemic tenecteplase. *Heart Lung Circ* 2008; 17: 253–5.

Ischaemic heart disease. Thrombolytics such as alteplase, streptokinase, and urokinase have an established role in the early management of acute myocardial infarction (p. 1257.1). Myocardial infarction is caused by coronary artery occlusion, usually due to thrombosis, and thrombolytics are given intravenously to break up the thrombus or clot and restore the patency of the coronary artery, thereby limiting infarct size and irreversible damage to the myocardium. Reduction of ECG abnormalities and modification of ventricular remodelling may also contribute to their effect. Other antithrombotics, in particular aspirin and heparin, are given as adjunctive therapy.

Several large studies have established that thrombolytics can preserve left ventricular function and improve short-term and 1-year mortality figures;[1,2] benefit has been maintained in 5-year[3] and 10-year[4,5] follow-up studies. Benefit is greatest with early treatment. Studies such as GISSI-1[6] and ISIS-2[7] helped to establish that mortality is reduced if thrombolytics are given within 6 hours of the onset of symptoms[8] and further studies provided evidence[9,10] that patients presenting within 12 hours should receive a thrombolytic. Use after 12 hours has been associated with an increase in adverse effects,[8] and is usually reserved for patients with evidence of ongoing ischaemia. Prehospital thrombolysis is feasible and reduces the time to thrombolysis and short-term mortality.[11] Five-year follow-up of one study[12] has suggested that there is also a beneficial effect on long-term mortality.

Choice of thrombolytic depends on factors such as cost, method of administration, and contra-indications. Although streptokinase has been the most widely used, several large studies have compared clinical benefit in terms of improved left ventricular function and mortality and have shown no difference between streptokinase and other thrombolytics, including saruplase,[13] the tissue plasminogen activator alteplase,[14] anistreplase,[15] and reteplase[16] in overall efficacy. In the GUSTO-I study,[17] accelerated or 'front loaded' alteplase (that is, rapid intravenous dosage over 1½ hours rather than the conventional 3 hours) was more effective than streptokinase, although the study was criticised for not comparing like with like. On the other hand, alteplase might be associated with a greater risk of stroke than streptokinase.[18] Studies comparing bolus injections of reteplase with accelerated alteplase (GUSTO-III)[19] and tenecteplase with alteplase (ASSENT-2)[20] have also found no difference in mortality rate.

The overall efficacy of thrombolytics is limited by persistent coronary occlusion, re-occlusion, and bleeding complications. Different thrombolytic regimens, such as bolus injections of reteplase, and combinations of thrombolytics, for example alteplase with streptokinase and alteplase with saruplase, have been investigated in attempts to improve patency rates. However, there has been concern that adverse effects may be higher with bolus injection. A study[21] comparing double-bolus alteplase with accelerated alteplase was terminated early when excess deaths were found in the group receiving bolus injections, and a subsequent meta-analysis[22] found a higher incidence of intracranial haemorrhage associated with bolus doses of various thrombolytics. Although use of thrombolytics before percutaneous coronary intervention (PCI) does not appear to be beneficial, a small study[23] has suggested that intracoronary streptokinase given immediately after PCI

may improve microvascular reperfusion; subsequent results[24] have suggested this may produce clinical benefit.

Thrombolytics have also been tried in other acute coronary syndromes, including unstable angina and non-ST elevation myocardial infarction (p. 1254.3). Although small-scale studies reported some benefit the results were variable, and an overview[8] of studies in patients with suspected myocardial infarction, which included some patients with unstable angina, found that there was no mortality benefit in patients without ST elevation. In 2 studies that investigated alteplase (the TIMI-IIIB study[25] with 1473 patients) and anistreplase (the UNASEM study[26] involving 159 patients), thrombolysis failed to improve outcome and was associated with an excess of bleeding complications. Thrombolytic therapy is therefore not recommended for patients with unstable angina or non-ST elevation myocardial infarction.

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. *Lancet* 1987; ii: 871–4.
2. Wilcox RG, *et al.* Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. *Lancet* 1990; 335: 1175–8.
3. Simoons ML, *et al.* Long-term benefit of early thrombolytic therapy in patients with acute myocardial infarction: 5 year follow-up of a trial conducted by the Interuniversity Cardiology Institute of the Netherlands. *J Am Coll Cardiol* 1989; 14: 1609–15.
4. Baigent C, *et al.* ISIS-2: 10 year survival among patients with suspected acute myocardial infarction in randomised comparison of intravenous streptokinase, oral aspirin, both, or neither. *BMJ* 1998; 316: 1337–43.
5. Franzosi MG, *et al.* Ten-year follow-up of the first megatrial testing thrombolytic therapy in patients with acute myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 Study. *Circulation* 1998; 98: 2659–65.
6. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; i: 397–402.
7. Second International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; ii: 349–60.
8. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994; 343: 311–22.
9. LATE Study Group. Late assessment of thrombolytic efficacy (LATE) study with alteplase 6–24 hours after onset of acute myocardial infarction. *Lancet* 1993; 342: 759–66.
10. EMERAS (Estudio Multicéntrico Estreptoquinasa Repúblicas de América del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 1993; 342: 767–72.
11. Morrison LJ, *et al.* Mortality and prehospital thrombolysis for acute myocardial infarction: a meta-analysis. *JAMA* 2000; 283: 2686–92.
12. Rawles JM. Quantification of the benefit of earlier thrombolytic therapy: five-year results of the Grampian Region Early Anistreplase Trial (GREAT). *J Am Coll Cardiol* 1997; 30: 1181–6.
13. PRIMI Trial Study Group. Randomised double-blind trial of recombinant pro-urokinase against streptokinase in acute myocardial infarction. *Lancet* 1989; i: 863–8.
14. GISSI-2 and International Study Group. Six-month survival in 20 891 patients with acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. *Eur Heart J* 1992; 13: 1692–7.
15. Third International Study of Infarct Survival Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41 299 cases of suspected acute myocardial infarction. *Lancet* 1992; 339: 753–70.
16. International Joint Efficacy Comparison of Thrombolytics. Randomised, double-blind comparison of reteplase double-bolus administration with streptokinase in acute myocardial infarction (INJECT): trial to investigate equivalence. *Lancet* 1995; 346: 329–36.
17. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; 329: 673–82.
18. Vaitkus PT, *et al.* Stroke complicating acute myocardial infarction: a meta-analysis of risk modification by anticoagulation and thrombolytic therapy. *Arch Intern Med* 1992; 152: 2020–4.
19. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med* 1997; 337: 1118–23.
20. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; 354: 716–22.
21. The Continuous Infusion versus Double-Bolus Administration of Alteplase (COBALT) Investigators. A comparison of continuous infusion of alteplase with double-bolus administration for acute myocardial infarction. *N Engl J Med* 1997; 337: 1124–30.
22. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; 356: 449–54.
23. Sezer M, *et al.* Intracoronary streptokinase after primary percutaneous coronary intervention. *N Engl J Med* 2007; 356: 1823–34.
24. Sezer M, *et al.* Effect of intracoronary streptokinase administered immediately after primary percutaneous coronary intervention on long-term left ventricular infarct size, volumes, and function. *J Am Coll Cardiol* 2009; 54: 1065–71.
25. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. *Circulation* 1994; 89: 1545–56.
26. Bär FW, *et al.* Thrombolysis in patients with unstable angina improves the angiographic but not the clinical outcome: results of UNASEM, a multicenter, randomized, placebo-controlled, clinical trial with anistreplase. *Circulation* 1992; 86: 131–7.

Peripheral arterial thromboembolism. Although surgery has been the first-line therapy for peripheral arterial thromboembolism (p. 1273.3), thrombolytics have an increasingly important role, either alone or as an adjunct to surgery or percutaneous interventions.[1] Streptokinase, given intravenously, effectively restores arterial patency in acute occlusion, but the high rate of bleeding complications limits use of this route.[2] Direct intra-arterial infusion (catheter-directed thrombolysis) appears to be more effective, particularly when the catheter is placed directly into the thrombus, and this technique is now preferred. Alternatively, intra-arterial thrombolytics may be used as adjunctive therapy to reduce the clot burden before or during surgical or percutaneous intervention or to treat distal clots.[1] The *intravenous* dose generally used is 250 000 units over 30 minutes followed by 100 000 units/hour. A lower dose of 5000 units/hour has been used *intra-arterially* directly into the clot,[3] and for removal of distal clots during surgery streptokinase has been given intra-arterially in a dose of 100 000 units over 30 minutes or as five bolus doses of 20 000 units at 5-minute intervals.[4]

Other thrombolytics are now more widely used than streptokinase, although relative efficacy of the different drugs is unclear.[5] Alteplase and urokinase are both used, and clinical practice now favours them over streptokinase;[3,6,7] positive results have also been reported with reteplase and tenecteplase.[7]

1. Norgren L, *et al.* Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). *J Vasc Surg* 2007; 45 (suppl S): S5–S67.
2. Kessel DO, *et al.* Infusion techniques for peripheral arterial thrombolysis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/08/09).
3. Giannini D, Balbarini A. Thrombolytic therapy in peripheral arterial disease. *Curr Drug Targets Cardiovasc Haematol Disord* 2004; 4: 249–58.
4. Earnshaw JJ, Beard JD. Intraoperative use of thrombolytic agents. *BMJ* 1993; 307: 638–9.
5. Robertson L, *et al.* Fibrinolytic agents for peripheral arterial occlusion. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 14/06/10).
6. Berridermacher BL, *et al.* Medical management of peripheral arterial disease. *J Thromb Haemost* 2005; 3: 1628–37.
7. Gray BH, *et al.* American Heart Association Writing Group 7. Atherosclerotic Peripheral Vascular Disease Symposium II: lower-extremity revascularization: state of the art. *Circulation* 2008; 118: 2864–72.

CENTRAL RETINAL ARTERY OCCLUSION. Central retinal artery occlusion may result in severe and permanent visual loss in the affected eye. The use of thrombolytics has been investigated for treatment, with variable results.

References.

1. Butz B, *et al.* Selective intraarterial fibrinolysis of acute central retinal artery occlusion. *Acta Radiol* 2003; 44: 680–4.
2. Arnold M, *et al.* Comparison of intra-arterial thrombolysis with conventional treatment in patients with acute central retinal artery occlusion. *J Neurol Neurosurg Psychiatry* 2005; 76: 196–9.
3. Pettersen JA, *et al.* Intra-arterial thrombolysis for retinal artery occlusion: the Calgary experience. *Can J Neurol Sci* 2005; 32: 507–11.
4. Biousse V, *et al.* Thrombolysis for central retinal artery occlusion. *J Neuroophthalmol* 2007; 27: 215–30.
5. Noble J, *et al.* Intra-arterial thrombolysis for central retinal artery occlusion: a systematic review. *Br J Ophthalmol* 2008; 92: 588–93.
6. Hattenbach LO, *et al.* Intravenous thrombolysis with low-dose recombinant tissue plasminogen activator in central retinal artery occlusion. *Am J Ophthalmol* 2008; 146: 700–6.
7. Aldrich EM, *et al.* Local intraarterial fibrinolysis administered in aliquots for the treatment of central retinal artery occlusion: the Johns Hopkins Hospital experience. *Stroke* 2008; 39: 1746–50.
8. Zhang X, *et al.* Intra-arterial thrombolysis for acute central retinal artery occlusion. *Neurol Res* 2009; 31: 385–9.

Stroke. Stroke (p. 1269.2) is normally considered a contra-indication to the use of thrombolytics, and clearly they would be inappropriate in acute haemorrhagic stroke. However, when stroke is associated with thrombotic occlusion there is evidence, as with myocardial infarction, that a degree of neuronal recovery is possible if the occlusion is reversed sufficiently quickly, and thrombolytics may therefore have a role in some patients with acute ischaemic stroke.

Early studies with intravenous thrombolytics in acute *ischaemic stroke* suggested a reduction in early death, although subsequent randomised trials produced disappointing results, with the exception of one with alteplase given within 3 hours of the onset of stroke (NINDS—National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial).[1] The studies using streptokinase—MAST-E (Multicentre Acute Stroke Trial-Europe),[2] ASK (Australian Streptokinase Trial),[3] and MAST-I (Multicentre Acute Stroke Trial-Italy)[4,5]—were terminated before completion because of adverse outcomes (intracranial bleeding and increased mortality) in the treatment groups, particularly in those receiving therapy more than 3 hours after stroke onset.[3] The study investigating alteplase given within 6 hours of the onset of symptoms (ECASS I—European Cooperative Acute Stroke Study)[6] reported that, although some patients might benefit, overall alteplase was associated with higher mortality rates and an increase in some intracranial bleeding (parenchymal haemorrhage). In the *NINDS* randomised study,[1] alteplase given within 3 hours of the onset of ischaemic stroke appeared to improve clinical outcome despite an increased incidence of symptomatic intracerebral haemorrhage. Patients treated with alteplase were more likely to have minimal or no disability 3 months after stroke,[1] and this benefit was maintained at 12 months.[7] However, there was no difference in mortality or rate of recurrence of stroke. A second ECASS study (ECASS II)[8] that hoped to confirm the early findings of the NINDS study failed to confirm a statistical benefit for alteplase over placebo and found no significant differences between patients who received alteplase within 3 hours or between 3 and 6 hours. A review[9] of several studies confirmed that alteplase needed to be given early, and preferably within 90 minutes, if it was to be effective.

On the basis of the NINDS study, alteplase given within 3 hours of the onset of ischaemic stroke is now recommended for selected patients in most guidelines on stroke management.[10-15] Despite their own disappointing results, the ECASS II investigators reached a similar conclusion. However, these recommendations have been criticised.[16,17]

It has been pointed out[18,19] that very few patients will be eligible for treatment with alteplase, since the time of onset of symptoms is often uncertain and in many patients more than 3 hours elapses before a definite diagnosis of ischaemic stroke is made. A later analysis of results from 6 major controlled studies found that benefits of alteplase treatment were greater than risks (in terms of number needed to treat versus number needed to harm) up to 4.5 hours after symptom onset; there was no evidence of net benefit in the period from 4.5 to 6 hours after onset.[20]

In addition, the *NINDS* study[1] excluded patients with severe stroke and those taking anticoagulants. The rationale for exclusion of patients with severe stroke is that haemorrhagic transformation is more likely to occur with large areas of infarction.[18] However, size of infarct is difficult to identify by CT scanning.[18] Anticoagulants or antiplatelets are also contra-indicated in the first 24 hours after use of alteplase. The poor results obtained in studies using streptokinase have led to recommendations that streptokinase should be avoided in ischaemic stroke,[13] although an overview of thrombolytic studies[19] suggested that it may not be worse than alteplase and that the apparent hazards of streptokinase may be accounted for by differences in trial design (for example use with anticoagulants) and in patient population.

A systematic review[21] therefore concluded that further large studies are required to establish more clearly the overall role of thrombolytics in acute ischaemic stroke. Studies of the use of alteplase outside the setting of a clinical trial have had mixed results.[22-24] However, an observational study[25] found that alteplase was safe and effective when used in accordance with guidelines, while another study[26] found that it could be used in elderly patients (80 years-of-age and older), a group normally excluded from clinical trials. Another observational study[27] suggested (in line with the analysis of numbers needed to treat[20] referred to above) that alteplase was safe given up to 4.5 hours after stroke onset, and a randomised study[28] found that alteplase also improved outcomes when given after 3 to 4.5 hours, although the authors stressed that treatment within 3 hours was still preferred.

Intra-arterial thrombolytics may have advantages over intravenous use and may be used in selected patients.[12-14] Studies with nasaruplase[29] and urokinase[30] have suggested benefit up to 6 hours after stroke due to middle cerebral artery occlusion, and use of intra-arterial thrombolytics may therefore be considered in such patients.[12-14] Intra-arterial thrombolytics are also used in basilar artery occlusion, although evidence to support this is limited;[12,13,31] intravenous alteplase may be an alternative.[32] Combined use of intravenous and intra-arterial alteplase,[33] as well as use of adjunctive therapies such as therapeutic ultrasound[34] or antithrombotics, are under investigation but do not yet have an established role.[13]

Intravenous thrombolytics have no role in the management of acute *haemorrhagic stroke*, but they have been given locally to facilitate the aspiration of haematomas in both intracerebral[35] and subarachnoid haemorrhage. Small studies with urokinase have shown benefit in patients with intraventricular haemorrhage.

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333: 1581–7.
2. The Multicenter Acute Stroke Trial—Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 1996; 335: 145–50.
3. Donnan GA, *et al.* Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA* 1996; 276: 961–6.
4. Multicentre Acute Stroke Trial - Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet* 1995; 346: 1509–14.
5. Tognoni G, Roncaglioni MC. Dissent: an alternative interpretation of MAST-I. *Lancet* 1995; 346: 1515.
6. Hacke W, *et al.* Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274: 1017–25.
7. Kwiatowski TG, *et al.* Effects of tissue plasminogen activator for acute ischemic stroke at one year. *N Engl J Med* 1999; 340: 1781–7.
8. Hacke W, *et al.* Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998; 352: 1245–51.
9. The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of

ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004; 363: 768–74.
10. The International Liaison Committee on Resuscitation (ILCOR). 2005 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Section 2: Stroke and first aid. Part 9: Stroke. *Circulation* 2005; 112 (suppl I): III110–III114. Also available at: http://Incl-circ.ahajournals.org/cgi/reprint/112/22_suppl/III-110 (accessed 01/03/06)
11. NICE. Alteplase for the treatment of acute ischaemic stroke: Technology Appraisal Guidance 122 (issued June 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA122guidance.pdf (accessed 30/04/08)
12. European Stroke Organisation (ESO) Executive Committee. ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; 25: 457–507. Also available at: http://www.eso-stroke.org/pdf/ESO08_Guidelines_English.pdf (accessed 11/07/08)
13. Adams HP, *et al.* Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. *Stroke* 2007; 38: 1655–1711. Also available at: http://stroke.ahajournals.org/cgi/reprint/38/5/1655.pdf (accessed 11/07/08)
14. Albers GW, *et al.* Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 630S–669S. Also available at: http://chestjournal.chestpubs.org/content/133/6_suppl/630S.full.pdf+html (accessed 03/08/10)
15. The Intercollegiate Stroke Working Party. National clinical guideline for stroke: third edition. London: Royal College of Physicians, 2008. Also available at: http://www.rcplondon.ac.uk/pubs/contents/6ad05aab-8400-494c-8cf4-9772d1d5301b.pdf (accessed 01/10/08)
16. Caplan LR. Stroke thrombolysis—growing pains. *Mayo Clin Proc* 1997; 72: 1090–2.
17. Caplan LR, *et al.* Should thrombolytic therapy be the first-line treatment for acute ischemic stroke? Thrombolysis—not a panacea for ischemic stroke. *N Engl J Med* 1997; 337: 1309–10.
18. Muir KW. Thrombolysis for stroke: pushed out of the window? *Br J Clin Pharmacol* 1996; 42: 681–2.
19. Wardlaw JM, *et al.* Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. *Lancet* 1997; 350: 607–14.
20. Lansberg MG, *et al.* Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke* 2009; 40: 2079–84.
21. Wardlaw JM, *et al.* Thrombolysis for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 04/08/10).
22. Albers GW, *et al.* Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) Study. *JAMA* 2000; 283: 1145–50.
23. Katzan IL, *et al.* Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA* 2000; 283: 1151–8.
24. Hill MD, Buchan AM. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *Can Med Assoc J* 2005; 172: 1307–12.
25. Wahlgren N, *et al.* Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; 369: 275–82.
26. Engelter ST, *et al.* Thrombolysis in stroke patients aged 80 years and older: Swiss survey of IV thrombolysis. *Neurology* 2005; 65: 1795–8.
27. Wahlgren N, *et al.* SITS Investigators. Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008; 372: 1303–9.
28. Hacke W, *et al.* ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; 359: 1317–29.
29. Furlan A, *et al.* Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *JAMA* 1999; 282: 2003–11.
30. Ogawa A, *et al.* Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke* 2007; 38: 2633–9.
31. Wijdicks EFM, *et al.* Intra-arterial thrombolysis in acute basilar artery thromboembolism: the initial Mayo Clinic experience. *Mayo Clin Proc* 1997; 72: 1005–13.
32. Lindsberg PJ, *et al.* Long-term outcome after intravenous thrombolysis of basilar artery occlusion. *JAMA* 2004; 292: 1862–6.
33. Flaherty ML, *et al.* Combined IV and intra-arterial thrombolysis for acute ischemic stroke. *Neurology* 2005; 64: 886–8.
34. Alexandrov AV, *et al.* Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med* 2004; 351: 2170–8.
35. Broderick JP, *et al.* Guidelines for the management of spontaneous intracerebral hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1999; 30: 905–15. Also available at: http://stroke.ahajournals.org/cgi/reprint/30/4/905.pdf (accessed 06/07/04)

Adverse Effects

In common with other thrombolytics streptokinase may cause haemorrhage, particularly from puncture sites; severe internal bleeding has occurred and may be difficult to control. Streptokinase is antigenic, and allergic reactions ranging from rashes to rarer anaphylactoid and serum-sickness-like symptoms have occurred. Fever, sometimes high, and associated symptoms such as chills and back or abdominal pain are quite frequent. Nausea and vomiting may occur. There have been a few reports of Guillain-Barré syndrome.

Streptokinase infusion may be associated with hypotension, both direct or as a result of reperfusion; bradycardia and arrhythmias may also occur due to reperfusion. The break-up of existing clots may occasionally produce emboli elsewhere; pulmonary embolism and acute renal failure due to cholesterol embolisation have been reported.

Back pain. Streptokinase infusion has been associated with the development of very severe low back pain, which resolves within a few minutes of stopping the infusion, and may be severe enough to warrant opioid analgesia.[1-4] The back pain may represent a hypersensitivity reaction. Providing that the pain is controlled and that dissecting aortic aneurysm is not suspected, it may still be possible to complete the streptokinase infusion.[4,5] Alternatively, immediate substitution with a different thrombolytic has been suggested.[6]

There have also been a few reports of low back pain associated with anistreplase infusion.[7,8]

1. Shah M, Taylor RT. Low back pain associated with streptokinase. *BMJ* 1990; 301: 1219.
2. Dickinson RJ, Rosser A. Low back pain associated with streptokinase. *BMJ* 1991; 302: 111–12.
3. Porter NJ, Nikoletatos K. Low back pain associated with streptokinase. *BMJ* 1991; 302: 112.
4. Pinheiro RF, *et al.* Low back pain during streptokinase infusion. *Arq Bras Cardiol* 2002; 78: 233–5.
5. Lear J, *et al.* Low back pain associated with streptokinase. *Lancet* 1992; 340: 851.
6. Fishwick D, *et al.* Thrombolysis and low back pain. *BMJ* 1995; 310: 504.
7. Hannaford P, Kay CR. Back pain and thrombolysis. *BMJ* 1992; 304: 915.
8. Lear J, Rajapakse R. Low back pain associated with anistreplase. *BMJ* 1993; 306: 896.

Effects on the blood. Although falls in the haemoglobin value of patients receiving thrombolytics are most likely to be due to blood loss from haemorrhage, there has been a report of a patient who had signs of haemolytic anaemia after intravenous infusion of streptokinase.[1] In a subsequent test *in vitro* the patient's serum caused strong agglutination of streptokinase-treated red blood cells, supporting the view that streptokinase was responsible for the haemolysis.

1. Mathiesen O, Grunnet N. Haemolysis after intravenous streptokinase. *Lancet* 1989; i: 1016–17.

Effects on the eyes. Acute uveitis[1,2] and iritis,[3,4] associated with transient renal impairment in one patient,[3] have followed treatment of myocardial infarction with intravenous streptokinase. In one case uveitis was associated with serum sickness[2] and in all of them hypersensitivity to streptokinase was suspected.

1. Kinshuck D. Bilateral hypopyon and streptokinase. *BMJ* 1992; 305: 1332.
2. Proctor BD, Joondeph BC. Bilateral anterior uveitis: a feature of streptokinase-induced serum sickness. *N Engl J Med* 1994; 330: 576–7.
3. Birnbaum Y, *et al.* Acute iritis and transient renal impairment following thrombolytic therapy for acute myocardial infarction. *Ann Pharmacother* 1993; 27: 1539–40.
4. Gray MY, Lazarus JH. Iritis after treatment with streptokinase. *BMJ* 1994; 309: 97.

Effects on the kidneys. Transient proteinuria has been reported after use of streptokinase. In some patients proteinuria and renal impairment have developed about 7 days after thrombolytic therapy and have been associated with a syndrome resembling serum sickness,[1,2] suggesting a delayed hypersensitivity reaction; a similar case in a patient receiving anistreplase was associated with Henoch-Schönlein-like vasculitis.[3] These delayed reactions should be distinguished from the transient and apparently self-limiting proteinuria that has been reported in some patients in the first 24 to 72 hours after beginning streptokinase.[4,5] Proteinuria within the first 24 hours has been attributed to deposition of an immune complex in the glomeruli,[6] although haemodynamic and neurohormonal changes associated with acute myocardial infarction may be responsible since proteinuria has occurred in patients not receiving thrombolytic therapy.[7,8]

Streptokinase infusion has also been associated with acute oliguric renal failure due to acute tubular necrosis, apparently as a result of hypotension during the infusion, in a patient with existing renovascular narrowing.[9] Interestingly, it has been pointed out that a variant streptokinase may be the pathogenic agent in glomerulonephritis occurring after *Streptococcus pyogenes* infection.[10]

Renal failure has developed as a consequence of streptokinase-induced cholesterol embolism, see under Embolism, below.

1. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; ii: 1398.
2. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; 335: 106.
3. Ali A, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; 335: 106–7.
4. Argent N, Adams PC. Proteinuria and thrombolytic agents. *Lancet* 1990; 335: 106.
5. More RS, Peacock P. Haematuria and proteinuria after thrombolytic therapy. *Lancet* 1990; 336: 1454.
6. Lynch M, *et al.* Proteinuria with streptokinase. *Lancet* 1993; 341: 1024.
7. Pickett TM, Hilton PJ. Proteinuria and streptokinase. *Lancet* 1993; 341: 1538.
8. von Eyben FE, *et al.* Albuminuria with or without streptokinase. *Lancet* 1993; 342: 365–6.
9. Kaira PA, *et al.* Acute tubular necrosis induced by coronary thrombolytic therapy. *Postgrad Med J* 1991; 67: 212.
10. Barnham M. Hypersensitivity and streptokinase. *Lancet* 1990; 335: 535.

Effects on the liver. Raised serum-alanine aminotransferase values, and in some cases raised aspartate aminotransferase activity, were seen more frequently in 95 patients who received streptokinase than in 94 given placebo as part of a study in patients with myocardial infarction.[1] The mechanism for the raised aminotransferase activity was not clear; a concomitant rise in γ-glutamyltransferase activity and bilirubin concentration suggested an hepatic source. Overt jaundice has been reported rarely.[2]

For references to rupture of the liver occurring during treatment with streptokinase, see Haemorrhage, below.

1. Maclennan AC, *et al.* Activities of aminotransferases after treatment with streptokinase for acute myocardial infarction. *BMJ* 1990; 301: 321–2.
2. Gómez Guindal JA, *et al.* Ictericia inducida por estreptocinasa. *Rev Esp Cardiol* 1999; 52: 1025–7.

Effects on the nervous system. There have been a few reports of Guillain-Barré syndrome after treatment with streptokinase.[1-4] Whether streptokinase was the cause is not certain although its antigenic properties do suggest that induction of an immunological reaction might be responsible.[3]

For discussion of cerebrovascular effects of streptokinase, see Haemorrhage, below.

1. Eden KV. Possible association of Guillain-Barré syndrome with thrombolytic therapy. *JAMA* 1983; 249: 2020–1.
2. Leaf DA, *et al.* Streptokinase and the Guillain-Barré syndrome. *Ann Intern Med* 1984; 100: 617.
3. Barnes D, Hughes RAC. Guillain-Barré syndrome after treatment with streptokinase. *BMJ* 1992; 304: 1225.
4. Taylor BV, *et al.* Guillain-Barré syndrome complicating treatment with streptokinase. *Med J Aust* 1995; 162: 214–15.

Effects on the respiratory system. Fatal acute respiratory distress syndrome occurred in a patient given streptokinase for pulmonary embolism.[1] It was suggested that streptokinase may have caused the pulmonary injury by altering vascular permeability due to generation of fibrinolytic products or via reperfusion oedema.

1. Martin TR, *et al.* Adult respiratory distress syndrome following thrombolytic therapy for pulmonary embolism. *Chest* 1983; 83: 151–3.

Effects on the skin. Rashes may occur as an allergic reaction to streptokinase. For a report of skin necrosis possibly associated with cholesterol embolisation, see Embolism, below.

Embolism. Thrombolytic therapy has occasionally and paradoxically been associated with further embolism. This may be due to clots that break away from the treated thrombus, or to cholesterol crystals released after removal of fibrin from atheromatous plaques by thrombolysis.

Fatal pulmonary embolism has been reported,[1] apparently due to breakaway from a deep-vein thrombus under treatment. However, comparative studies have suggested that there is no evidence of a higher rate of such complications with streptokinase than with heparin.[2] When they do occur a good clinical response is usually seen to continued streptokinase.[2] Complications due to multiple microemboli were reported[3] in 7 of 475 consecutive patients treated with streptokinase or anistreplase for acute myocardial infarction. The sites of embolism were the legs (in 4) and brain (in 3); one patient apparently had systemic effects with skin infarction and renal impairment. Five of the 7 patients died. There has also been a report[4] of acute peripheral arterial thromboembolism in a patient given alteplase for ischaemic stroke.

Cholesterol embolisation can have many clinical manifestations depending on the location of the emboli. A classic presentation is livedo reticularis, gangrenous lower extremities, and acute renal failure.[5,6] Symptoms may appear within a few hours of starting thrombolytic treatment,[7] although in some cases they may not become evident for several days.[8-11]

1. Hill LN. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; 90: 411–12.
2. Rogers LQ, Lutcher CL. Streptokinase therapy and breakaway pulmonary emboli. *Am J Med* 1991; 90: 412–13.
3. Stafford PJ, *et al.* Multiple microemboli after disintegration of clot during thrombolysis for acute myocardial infarction. *BMJ* 1989; 299: 1310–12.
4. Gomez-Beldarrain M, *et al.* Peripheral arterial embolism during thrombolysis for stroke. *Neurology* 2006; 67: 1096–7.
5. Blankenship JC. Cholesterol embolisation after thrombolytic therapy. *Drug Safety* 1996; 14: 78–84.
6. Wong FKM, *et al.* Acute renal failure after streptokinase therapy in a patient with acute myocardial infarction. *Am J Kidney Dis* 1995; 26: 508–10.
7. Pochmalicki G, *et al.* Cholesterol embolisation syndrome after thrombolytic therapy for myocardial infarction. *Lancet* 1992; 339: 58–9.
8. Ridker PM, Michel T. Streptokinase therapy and cholesterol embolization. *Am J Med* 1989; 87: 357–8.
9. Pirson Y, *et al.* Cholesterol embolism in a renal graft after treatment with streptokinase. *BMJ* 1988; 296: 394–5.
10. Dass H, Fescharek R. Skin necrosis induced by streptokinase. *BMJ* 1994; 309: 1513–14.
11. Penswick J, Wright AL. Skin necrosis induced by streptokinase. *BMJ* 1994; 309: 378.

Haemorrhage. Haemorrhage is a common adverse effect of thrombolytic therapy, and the problem and its management have been reviewed.[1] Thrombolytics are used to lyse pathological thrombi, but can also produce a 'lytic state' due to depletion of the natural plasmin inhibitor α_2-antiplasmin by excess plasmin production, thus predisposing to severe bleeding; they may also cause lysis of thrombi required for haemostasis.

Haemorrhage is a particular risk where there is existing or concomitant trauma. More than 70% of bleeding

episodes occur at vascular puncture sites,[1] so invasive procedures should be avoided if possible; if catheterisation is considered essential meticulous care of the vascular puncture site is necessary. Bleeding or severe bruising in patients receiving thrombolytic therapy have also been associated with intramuscular injection of analgesics,[2] the use of an automatic blood-pressure measuring machine,[3] a pre-existing prosthetic abdominal aortic graft,[4] and recent dental extraction.[5] Other disease states may also contribute: haemospermia has been reported after thrombolysis in a patient with mild prostatic symptoms,[6] haemorrhagic bullae have been reported in a patient with lichen sclerosus et atrophicus,[7] and diabetic patients are at risk of retinal haemorrhage if they have diabetic retinopathy,[8] although any increase in risk seems to be small.[9] A review of the GUSTO-I Study[10] (40 903 patients) identified older age, low body-weight, female sex, and African ancestry as other factors that increased the risk of haemorrhage.

Intracranial haemorrhage leading to stroke is the most serious bleeding complication with thrombolytics, and has a high mortality. Assessment of data from national registries and large-scale studies has identified several risk factors for intracranial haemorrhage, including those mentioned above for overall haemorrhage, hypertension on admission, a history of stroke, and thrombolysis with current alteplase regimens.[11-14] The benefits and risks must be assessed for each patient and thrombolytic therapy should still be given to the elderly and to those with hypertension if the expected benefits are great. Intracranial haemorrhage is a particular concern with the use of thrombolytics for the treatment of ischaemic stroke. In the NINDS study, using alteplase, clinical outcome appeared to be improved despite an increased incidence of symptomatic intracerebral haemorrhage. Subgroup analysis[15] suggested that severe neurological deficit, brain oedema, and mass effect, before treatment, were risks associated with the increased incidence of haemorrhage.

Fibrin-specific thrombolytics such as alteplase were developed in the hope that they would have less systemic effect than fibrin-nonspecific thrombolytics such as streptokinase and therefore cause less bleeding. However, studies that have assessed comparative bleeding rates have failed to confirm this, although the use of adjunctive antithrombotics and different dose regimens makes comparison difficult. In GUSTO-I,[10] the bleeding rate with alteplase plus intravenous heparin was lower than with streptokinase plus intravenous heparin, but was similar to that with streptokinase plus subcutaneous heparin. However, the rate of intracranial haemorrhage was higher with alteplase.[16] In ASSENT-2,[17] which compared bolus doses of the highly fibrin-specific thrombolytic tenecteplase with front-loaded alteplase, tenecteplase produced fewer major non-cerebral bleeds than alteplase but the rates of intracranial haemorrhage were nearly identical. Although a meta-analysis[18] suggested that rates of intracranial haemorrhage may be higher with bolus thrombolytics, others have suggested that this may not be a problem with newer bolus regimens.[19]

Other bleeding complications reported with thrombolytics include rupture of the spleen[20,21] and liver,[22] and rupture of a follicle has been reported in a menstruating woman.[23] Rupture of the heart with fatal consequences has been reported, although thrombolytics do not appear to increase the overall risk of cardiac rupture following myocardial infarction,[24] except possibly for early rupture in women.[25]

Diffuse alveolar haemorrhage,[26] ventricular wall haematoma,[27] and spinal epidural haematoma[28] have been reported in patients treated with streptokinase after myocardial infarction. Intrapleural use was associated with life-threatening haemorrhage in empyema after cardiac surgery,[29] and with fatal haemorrhage in a case of aortic dissection misdiagnosed as empyema.[30]

1. Sane DC, *et al.* Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med* 1989; 111: 1010–22.
2. Morris GC, Sterry MJG. case report]. *BMJ* 1991; 302: 246.
3. Gibson P. case report]. *BMJ* 1991; 302: 1412.
4. London NJM, *et al.* Systemic thrombolysis causing haemorrhage around a prosthetic abdominal aortic graft. *BMJ* 1993; 306: 1530–1.
5. Lustig JP, *et al.* Thrombolytic therapy for acute myocardial infarction after oral surgery. *Oral Surg Oral Med Oral Pathol* 1993; 75: 547–8.
6. Keeling PJ, Lawson CS. Haemospermia: a complication of thrombolytic therapy. *Br J Hosp Med* 1990; 44: 244.
7. Dunn HM, Fulton RA. Haemorrhagic bullae in a patient with lichen sclerosus et atrophicus treated with streptokinase. *Heart* 1996; 76: 448.
8. Caramelli B, *et al.* Retinal haemorrhage after thrombolytic therapy. *Lancet* 1991; 337: 1356–7.
9. Ward H, Yudkin JS. Thrombolysis in patients with diabetes. *BMJ* 1995; 310: 3–4.
10. Berkowitz SD, *et al.* Incidence and predictors of bleeding after contemporary thrombolytic therapy for myocardial infarction. *Circulation* 1997; 95: 2508–16.
11. Simoons ML, *et al.* Individual risk assessment for intracranial haemorrhage during thrombolytic therapy. *Lancet* 1993; 342: 1523–8.
12. Aylward PE, *et al.* Relation of increased arterial blood pressure to mortality and stroke in the context of contemporary thrombolytic therapy for acute myocardial infarction: a randomized trial. *Ann Intern Med* 1996; 125: 891–900.
13. Bovill EG, *et al.* Hemorrhagic events during therapy with recombinant tissue plasminogen activator, heparin, and aspirin for unstable angina (Thrombolysis in Myocardial Ischemia, Phase IIIB trial). *Am J Cardiol* 1997; 79: 391–6.
14. Gurwitz JH, *et al.* Risk for intracranial hemorrhage after tissue plasminogen activator treatment for acute myocardial infarction. *Ann Intern Med* 1998; 129: 597–604.
15. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997; 28: 2109–18.
16. Gore JM, *et al.* Stroke after thrombolysis: mortality and functional outcomes in the GUSTO-I trial. *Circulation* 1995; 92: 2811–18.
17. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; 354: 716–22.
18. Mehta SR, *et al.* Risk of intracranial haemorrhage with bolus versus infusion thrombolytic therapy: a meta-analysis. *Lancet* 2000; 356: 449–54.
19. Armstrong PW, *et al.* Bolus fibrinolysis: risk, benefit, and opportunities. *Circulation* 2001; 103: 1171–3.
20. Wiener RS, Ong LS. Streptokinase and splenic rupture. *Am J Med* 1989; 86: 249.
21. Blankenship JC, Indeck M. Spontaneous splenic rupture complicating anticoagulant or thrombolytic therapy. *Am J Med* 1993; 94: 433–7.
22. Eklöf B, *et al.* Spontaneous rupture of liver and spleen with severe intra-abdominal bleeding during streptokinase treatment of deep venous thrombosis. *Vasa* 1977; 6: 369–71.
23. Müller C-H, *et al.* Near-fatal intra-abdominal bleeding from a ruptured follicle during thrombolytic therapy. *Lancet* 1996; 347: 1697.
24. Massel DR. How sound is the evidence that thrombolysis increases the risk of cardiac rupture? *Br Heart J* 1993; 69: 284–7.
25. Becker RC, *et al.* Fatal cardiac rupture among patients treated with thrombolytic agents and adjunctive thrombin antagonists: observations from the Thrombolysis and Thrombin Inhibition in Myocardial Infarction 9 Study. *J Am Coll Cardiol* 1999; 33: 479–87.
26. Yigla M, *et al.* Diffuse alveolar hemorrhage following thrombolytic therapy for acute myocardial infarction. *Respiration* 2000; 67: 445–8.
27. Mohamed HA, *et al.* Right ventricular wall hematoma due to thrombolytic therapy presenting as cardiac tamponade: a case report and review of literature. *Can J Cardiol* 2003; 19: 581–4.
28. Ozgocmen S, *et al.* Spinal epidural hematoma associated with streptokinase treatment for myocardial infarction. *Spinal Cord* 2004; 42: 374–7.
29. Porter J, Banning AP. Intrapleural streptokinase. *Thorax* 1998; 53: 720.
30. Srivastava P, *et al.* Fatal haemorrhage from aortic dissection following instillation of intrapleural streptokinase. *Scott Med J* 2000; 45: 86–7.

Hypersensitivity. Streptokinase is a bacterial protein and has antigenic activity. The formation of streptokinase-neutralising antibodies may reduce the efficacy of subsequent doses and increase the risk of hypersensitivity reactions.

In a series of 25 patients given intravenous streptokinase for myocardial infarction, titres of streptokinase-neutralising antibodies rose from a mean neutralisation capacity of 0.16 million units before treatment to a mean of 25.54 million units 2 weeks after treatment, the highest individual titre being 93 million units. After 12 weeks the neutralisation capacity was still sufficient in 24 patients to have neutralised a standard 1.5-million unit dose of streptokinase. After 17 to 34 weeks titres were still high enough in 18 of 20 patients examined to neutralise at least half a standard dose.[1] As these results indicate, giving standard doses of streptokinase within several months of a previous course may lead to reduced effect. Thus, the recommended period in which it should not be repeated is usually between 5 days and 1 year after the initial dose (see Precautions, below). However, high titres of neutralising antibodies persisting for up to 7.5 years after use of streptokinase have been reported.[2-4] Since repeated dosage also increases the risk of hypersensitivity reactions, it has been suggested[2,3] that repeat courses should not be given within 4 or more years, and that if a repeat course is needed a non-antigenic thrombolytic such as alteplase or urokinase should be used until it is known whether or not high *in-vitro* titres affect efficacy. Increased titres of streptokinase-neutralising antibodies have also been measured in patients given topical streptokinase for wounds.[6]

Anistreplase also appears susceptible to neutralisation by streptokinase antibodies.[7]

Plasmacytosis,[8,9] serum-sickness,[8,10,11] rhabdomyolysis,[12] renal impairment (see Effects on the Kidneys, p. 1505.2), uveitis and iritis (see Effects on the Eyes, p. 1505.2), arthritis,[13] and anaphylaxis[14-17] have been reported in patients given streptokinase and are thought to represent hypersensitivity reactions, in some cases perhaps due to previous exposure to streptococcal antigens during infection. Back pain (see p. 1505.1) may also represent a hypersensitivity reaction. In some patients there may be a delay of between 1 and 10 days before the reaction appears.[18] The incidence of severe hypersensitivity reactions is probably fairly low, however; in the GISSI study anaphylaxis was reported in only 7 of 5860 patients although other hypersensitivity reactions leading to withdrawal of streptokinase were reported in 99 patients, with a further 42 such reactions after completion of the infusion.[15] Some episodes of apparent anaphylaxis seen with streptokinase may be fibrinolysin-mediated rather than antibody-antigen reactions. Alteplase, which is considered non-antigenic, has produced an anaphylactoid reaction in patients with a history of atopy.[19,20] Angioedema also occurred[21] in a patient with a history of SLE and penicillin allergy who was given alteplase for deep-vein thrombosis. Fibrinolysin, which activates complement cascade and the kinin system, is formed in quantity after the use of a thrombolytic. In most patients these effects are clinically insignificant, but the possibility of precipitating an anaphylactoid reaction exists, especially in those who are strongly atopic. The risk of angioedema with alteplase may also be increased in those taking ACE inhibitors—see under Interactions of Alteplase, p. 1298.1.

1. Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; 335: 184–5.
2. Elliott JM, *et al.* Neutralizing antibodies to streptokinase four years after intravenous thrombolytic therapy. *Am J Cardiol* 1993; 71: 640–5.
3. Lee RS, *et al.* Raised levels of antistreptokinase antibody and neutralization titres from 4 days to 54 months after administration of streptokinase or anistreplase. *Eur Heart J* 1993; 14: 84–9.
4. Squire IB, *et al.* Humoral and cellular immune responses up to 7.5 years after administration of streptokinase for acute myocardial infarction. *Eur Heart J* 1999; 20: 1245–52.
5. Jennings K. Antibodies to streptokinase. *BMJ* 1996; 312: 393–4.
6. Green C. Antistreptokinase titres after topical streptokinase. *Lancet* 1993; 341: 1602–3.
7. Binette MJ, Agnone FA. Failure of APSAC thrombolysis. *Ann Intern Med* 1993; 119: 637.
8. Straub PW, *et al.* Plasmozytose nach thrombolytischer Therapie mit Streptokinase. *Schweiz Med Wochenschr* 1974; 104: 1891–2.
9. Chan NS, *et al.* Plasmacytosis and renal failure after readministration of streptokinase for threatened myocardial reinfarction. *BMJ* 1988; 297: 717–18.
10. Payne ST, *et al.* Transient impairment of renal function after streptokinase therapy. *Lancet* 1989; ii: 1398.
11. Callan MFC, *et al.* Proteinuria and thrombolytic agents. *Lancet* 1990; 335: 106.
12. Montgomery HE, *et al.* Rhabdomyolysis and multiple system organ failure with streptokinase. *BMJ* 1995; 311: 1472.
13. Kelly MP, Bielawska C. Recurrence of a reactive arthritis following streptokinase therapy. *Postgrad Med J* 1991; 67: 402.
14. McGrath KG, Patterson R. Anaphylactic reactivity to streptokinase. *JAMA* 1984; 252: 1314–17.
15. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; i: 397–401.
16. Bednarczyk EM, *et al.* Anaphylactic reaction to streptokinase with first exposure: case report and review of the literature. *DICP Ann Pharmacother* 1989; 23: 869–72.
17. Tisdale JE, *et al.* Streptokinase-induced anaphylaxis. *DICP Ann Pharmacother* 1989; 23: 984–7.
18. Seibert WJ, *et al.* Streptokinase morbidity—more common than previously recognised. *Aust N Z J Med* 1992; 22: 129–33.
19. Purvis JA, *et al.* Anaphylactoid reaction after injection of alteplase. *Lancet* 1993; 341: 966–7.
20. Massel D, *et al.* Anaphylactoid reaction during an infusion of recombinant tissue-type plasminogen activator for acute myocardial infarction. *Can J Cardiol* 1991; 7: 298–302.
21. Francis CW, *et al.* Angioedema during therapy with recombinant tissue plasminogen activator. *Br J Haematol* 1991; 77: 562–3.

Treatment of Adverse Effects

Allergic reactions to streptokinase may require treatment with antihistamines and corticosteroids, which have sometimes been given prophylactically. Anaphylaxis requires the use of adrenaline (for further details, see p. 1293.2).

Severe haemorrhage not controlled by local pressure requires the streptokinase infusion to be stopped. Tranexamic acid, aminocaproic acid, or aprotinin may be of benefit. Packed red blood cells may be preferable to whole blood for replacement therapy; factor VIII preparations may also be given. Volume expansion may be necessary, but the use of dextrans should be avoided because of their platelet-inhibiting properties.

Precautions

Streptokinase should be used with great care, if at all, in patients at increased risk of bleeding, or those in whom haemorrhage is likely to prove particularly dangerous. It should thus be avoided in patients with active internal bleeding or a recent history of peptic ulcer disease, oesophageal varices, ulcerative colitis or other bleeding gastrointestinal lesions, in patients with pancreatitis, in patients with subacute bacterial endocarditis, in patients with coagulation defects including those due to liver or kidney disease, or after recent surgery, childbirth, or trauma. It should not be given to patients at increased risk of cerebral bleeding including those with severe hypertension, haemorrhage or recent stroke, or to patients with cerebral neoplasm. It should not be given in pregnancy, particularly in the first 18 weeks because of the risk of placental separation and it has been suggested that it should not be used during heavy vaginal bleeding.

Invasive procedures, including intramuscular injections, should be avoided during, and immediately before and after, streptokinase therapy as they may increase the risk of bleeding; care should be taken when physically handling patients. Streptokinase should also be used with care in elderly patients. Patients with mitral stenosis associated with atrial fibrillation are more likely to have left heart thrombus which may lead to cerebral embolism after thrombolytic therapy. Although there is a theoretical risk of retinal bleeding in patients with diabetic retinopathy the benefits of treatment generally outweigh the risk.

Anti-streptokinase antibodies are formed after streptokinase use, with antibody titres rising abruptly after about 5 days. These antibodies may cause resistance or hypersensitivity to subsequent doses of streptokinase. Therefore,

further doses of streptokinase should not be given in the period between 5 days and 12 months after the initial dose (even longer periods have been suggested, see Hypersensitivity, under Adverse Effects, p. 1506.2); if thrombolytic therapy is required in this period an alternative non-antigenic drug should be used. High titres of anti-streptokinase antibodies may also occur in patients after some streptococcal infections such as streptococcal pharyngitis or acute rheumatic fever or in those with acute glomerulonephritis secondary to streptococcal infections; in such patients there may be resistance to streptokinase or a reduced effect.

Administration. Overinfusion of streptokinase may occur if a drop-counting infusion pump is used.[1] This arises as a result of flocculation of the streptokinase solution producing translucent fibres that affect the drop-forming mechanism so increasing the drop size.

For a comment on the incidence of flocculation in streptokinase solutions, see Stability, p. 1503.1.

1. Schad RF, Jennings RH. Overinfusions of streptokinase. *Am J Hosp Pharm* 1982; 39: 1850.

Aortic dissection. A report of 4 cases of the inappropriate use of streptokinase in patients with aortic dissection misdiagnosed as myocardial infarction.[1] Thrombolytics are likely to extend aortic dissection and adversely affect the outcome. Of the 2 patients who died, one, who would have been suitable for early operation, died through the delay caused by impaired clotting. Although early intervention with thrombolytics may be of major benefit in acute myocardial infarction it is important that accurate differential diagnosis takes place to exclude conditions such as aortic dissection and prevent avoidable deaths.

For a report of fatal haemorrhage with streptokinase used in aortic dissection misdiagnosed as empyema, see Haemorrhage under Adverse Effects, p. 1505.3.

1. Butler J, *et al.* Streptokinase in acute aortic dissection. *BMJ* 1990; 300: 517–19.

Cardiopulmonary resuscitation. Thrombolytics are not recommended after prolonged or traumatic cardiopulmonary resuscitation because of the risk of haemorrhage. However, studies[1,2] in patients given cardiopulmonary resuscitation for cardiac arrest associated with acute myocardial infarction have suggested that thrombolytics are generally safe and that any increase in bleeding complications is outweighed by the benefits of thrombolysis.

1. Cross SJ, *et al.* Safety of thrombolysis in association with cardiopulmonary resuscitation. *BMJ* 1991; 303: 1242.
2. Kurkciyan I, *et al.* Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. *J Intern Med* 2003; 253: 128–35.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies streptokinase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pregnancy. Thrombolytics are generally contra-indicated in pregnancy. However there are a few reports of their use and these have been briefly reviewed.[1] In most cases, thrombolytics were given at 28 weeks of pregnancy or later to patients with deep-vein thrombosis, pulmonary embolism, or prosthetic valve thrombosis. There were some reports of favourable maternal and fetal outcomes although therapy was associated with maternal haemorrhage, including spontaneous abortion and minor vaginal bleeding, especially when given near the time of delivery. There was one report of placental abruption with fetal death. A later review[2] noted about 200 successful cases of thrombolytic treatment in pregnancy, with a maternal mortality of about 1%, fetal mortality of about 6%, and premature delivery of about 6%. US guidelines[3] recommend reserving thrombolytic therapy in pregnant patients for life-threatening instances of thromboembolism.

1. Roth A, Elkayam U. Acute myocardial infarction associated with pregnancy. *Ann Intern Med* 1996; 125: 751–62.
2. Ahearn GS, *et al.* Massive pulmonary embolism during pregnancy successfully treated with recombinant tissue plasminogen activator: a case report and review of treatment options. *Arch Intern Med* 2002; 162: 1221–7.
3. Bates SM, *et al.* American College of Chest Physicians. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133 (suppl): 844S–886S. Also available at: http://www.chestjournal.org/content/133/6_suppl/844S.full.pdf (accessed 14/10/09)

Interactions

Oral anticoagulants, heparin, and antiplatelet drugs such as aspirin are often used with streptokinase, but may increase the risk of haemorrhage. The risk may also be increased with dextrans, and with other drugs that affect coagulation or platelet function.

References.
1. Harder S, Klinkhardt U. Thrombolytics: drug interactions of clinical significance. *Drug Safety* 2000; 23: 391–9.

Pharmacokinetics

Streptokinase is rapidly cleared from the circulation after intravenous use. Clearance is biphasic with the initial and more rapid phase being due to specific antibodies. A half-life of 23 minutes has been reported for the streptokinase-activator complex.

References.
1. Grierson DS, Bjornsson TD. Pharmacokinetics of streptokinase in patients based on amidolytic activator complex activity. *Clin Pharmacol Ther* 1987; 41: 304–13.
2. Gemmill JD, *et al.* A comparison of the pharmacokinetic properties of streptokinase and anistreplase in acute myocardial infarction. *Br J Clin Pharmacol* 1991; 31: 143–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Streptase; *Austral.*: Streptase†; *Belg.*: Streptase†; *Braz.*: Solustrep; Streptase; Streptokin; Streptonase†; *Canad.*: Streptase†; *Chile*: Thromboflux; *China*: Sikaitong (思凯通); Streptase (慧链); Xin Tong (欣通); *Cz.*: Streptase; *Denm.*: Streptase; *Fr.*: Streptase; *Ger.*: Streptase; *Gr.*: Kabikinase; Streptase; *Hong Kong*: Streptase; *Hung.*: Streptase; *India*: Cardiostrep; Eskinase; Fibrokinase; Haemokinase; Icikinase; Kabikinase; Myokinase; Niskinase; STpase; Streptase; Zykinase; *Indon.*: Streptase; *Israel*: Streptase; *Mex.*: Streptase; *Neth.*: Streptase; *NZ*: Streptase; *Philipp.*: ST-Pase; Streptokin; Thromboflux; *Pol.*: Streptase; *Port.*: Streptase; *Rus.*: Streptase (Стрептаза); Thromboflux (Тромбофлюкс); *S.Afr.*: Streptase; *Singapore*: Streptase; *Spain*: Streptase†; *Swed.*: Streptase; *Switz.*: Streptase†; *Thai.*: Streptase; Thromboflux; *Turk.*: Kabikinase; Streptase; *UK*: Streptase; *Ukr.*: Farmakinaza (Фармакиназа); *USA*: Streptase; *Venez.*: Streptase.

Multi-ingredient Preparations. *Austria*: Varidase; *Fin.*: Varidase†; *Ger.*: Varidase; *Mex.*: Varidasa; *Norw.*: Varidase†; *Pol.*: Biostreptaza; Distreptaza; *Spain*: Ernodasa; Varidasa; *Ukr.*: Biostrepta (Биострепта); Distreptaza (Дистрептаза).

Pharmacopoeial Preparations

BP 2014: Streptokinase Injection.

Strophanthin-K

Estrofantina; Kombé Strophanthin; Strophanthin; Strophanthoside-K; Строфантин-К

CAS — 11005-63-3.

NOTE. Do not confuse with K-strophanthin-α which is Cymarin.

Pharmacopoeias. In *Chin.*

Profile

Strophanthin-K is a cardiac glycoside or a mixture of cardiac glycosides from strophanthus, the seeds of *Strophanthus kombe* (Apocynaceae) or other spp., adjusted by admixture with a suitable diluent such as lactose so as generally to possess 40% of the activity of anhydrous ouabain.

Strophanthin-K is a positive inotrope with general properties similar to those of digoxin (p. 1353.3). It is poorly absorbed from the gastrointestinal tract but may be given intravenously in maintenance doses of 125 to 250 micrograms daily in the management of heart failure (p. 1262.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Kombetin.

Homoeopathic Preparations. *Austria*: Barium Med Complex; Corasan; Lakrima; *Fr.*: Soludor; *Ger.*: Cor Plus; Cor; Corvipas SL; Habstal-Cor N; Myonasan.

Suleparoid *(rINNM)*

Heparan Sulfate; Heparan Sulphate; Heparansulfat; Heparitin Sulfate; Siarczan Heparanu; Suleparoide; Suléparoïde; Suleparoidum; Sulfate d'Héparane; Сулепароид

CAS — 9050-30-0.

UNII — 47959853RS.

Suleparoid Sodium *(rINN)*

Heparan Sulfate Sodium; Sodium Heparitin Sulphate; Suleparoide sódico; Suléparoïde Sodique; Suleparoidum Natricum; Сулепароид Натрий

CAS — 57459-72-0.

Profile

Suleparoid is a naturally occurring glycosaminoglycan used topically in the management of haematomas and superficial thromboses, and for the relief of sprains and contusions. It has also been given orally. Suleparoid sodium is a component of danaparoid sodium (p. 1349.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Aremin; Clarema; Hemovasal; Vas†.

Multi-ingredient Preparations. *Ital.*: Osmogel.

Sulodexide *(rINN)*

KRX-101; Sulodeksyd; Sulodexida; Sulodexidum; Сулодексид

Glucurono-2-amino-2-deoxyglucoglucan sulfate.

CAS — 57821-29-1.

ATC — B01AB11.

ATC Vet — QB01AB11.

Profile

Sulodexide is a heparinoid consisting of a mixture of low-molecular-weight heparin and dermatan sulfate. It is used as a hypolipidaemic and antithrombotic and has been given orally and parenterally for peripheral vascular disease and cerebrovascular disease. It is also included in preparations used topically for local vascular inflammation and soft-tissue disorders. Sulodexide has also been investigated for other disorders including the treatment of diabetic nephropathy.

References.
1. Ofosu FA. Pharmacological actions of sulodexide. *Semin Thromb Hemost* 1998; 24: 127–38.
2. Weiss R, *et al.* The role of sulodexide in the treatment of diabetic nephropathy. *Drugs* 2007; 67: 2681–96.
3. Neri G, *et al.* Management of tinnitus: oral treatment with melatonin and sulodexide. *J Biol Regul Homeost Agents* 2009; 23: 103–10.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Vessel Due F (伟素); *Cz.*: Vessel Due F; *Hung.*: Vessel Due F; *Ital.*: Angioflux; Clarens; Provenal; Ravenol; Treparin; Vessel; *Malaysia*: Vessel Due F; *Philipp.*: Vessel Due F; *Pol.*: Vessel Due F; *Port.*: Vessel; *Rus.*: Angioflux (Ангиофлюкс); Vessel Due F (Вессел Дуэ Ф); *Spain*: Aterina; *Thai.*: Vessel; *Turk.*: Anjioflux; *Venez.*: Vessel Due.

Sympathomimetics ⊗

Actions and Uses

Sympathomimetics have actions that mimic the effects of stimulation of postganglionic (adrenergic) nerves. They include the endogenous catecholamines adrenaline, noradrenaline, and dopamine, and other drugs that directly stimulate adrenergic receptors, as well as drugs that have an indirect action by stimulating the release of noradrenaline from storage vesicles in adrenergic nerve endings. Phenylephrine is an example of a direct-acting sympathomimetic, whereas ephedrine and many other sympathomimetics have both direct and indirect effects.

The endogenous sympathomimetics are catecholamines, consisting of a catechol portion (characterised by hydroxy groups at adjacent positions on a benzene ring) and an aliphatic amine portion. Adrenaline and noradrenaline both have direct actions on adrenergic receptors, whereas dopamine has direct and indirect actions, as well as stimulating specific dopamine receptors. Although sympathetic nerves are generally termed adrenergic, the principal neurotransmitter is actually noradrenaline; it also acts as a neurotransmitter in the CNS. The major physiological role of adrenaline is metabolic. Dopamine is an important neurotransmitter within the CNS, but also has a role peripherally within the renal, mesenteric, and coronary vasculature.

Adrenergic receptors are classified as either alpha or beta receptors, and these are subdivided into several types. Dopamine receptors are a distinct group of receptors that are mainly found in the CNS, and at least 5 subtypes are known (see p. 889.1); D_1 receptors also occur in some vascular beds. The effects of adrenergic stimulation depend on the location and activity of the receptors:

- $alpha_1$ receptors are found mainly in blood vessels, as well as in the skin, eye, bladder, uterus, and liver. Stimulation leads to vasoconstriction, particularly in the vessels of the skin and mucosa, abdominal viscera, and kidney; this results in an increase in blood pressure, sometimes with compensatory reflex bradycardia. $Alpha_1$ stimulation also results in contraction of other smooth muscle, including the urinary sphincter and the uterus, and induces mydriasis in the eye

- alpha$_2$ receptors are mainly found presynaptically. Stimulation appears to play a role in feedback inhibition of neurotransmitter release and may be involved in the inhibition of intestinal activity; it also plays a role in the inhibition of insulin secretion
- beta$_1$ receptors are found mainly in the heart. Stimulation produces an increase in the rate and force of contraction, increased conduction velocity, and greater automaticity
- beta$_2$ receptors are mainly found in blood vessels and the lung, as well as in the uterus, the gastrointestinal tract, the liver, and the ciliary body of the eye. Stimulation leads to vasodilatation, bronchodilatation, uterine relaxation, and a decrease in gastrointestinal motility; it also results in release of insulin and enhances gluconeogenesis and glycogenolysis
- beta$_3$ receptors are found in fat cells and are thought to have a role in lipolysis and thermogenesis; they have also been found in the heart, uterus, and bladder but their role is not clear
- D_1 receptors are found in the renal, mesenteric, and coronary vascular beds. Stimulation leads to vasodilatation

Sympathomimetics differ in their relative affinity for each type of receptor, and also in whether they have direct or indirect actions (see Table 5, below). Their effects generally reflect these characteristics, although both may depend on the dose. Feedback mechanisms and the homoeostatic response of the body are also important. The specific effects of the different sympathomimetics are described in more detail in the individual monographs.

The endogenous catecholamines all have a very short action and are inactive orally; they are also highly polar and do not cross the blood-brain barrier. Other sympathomimetics are analogues of catecholamines but generally have a longer duration of action and are orally active; many also cross the blood-brain barrier and have central effects. For example, dexamfetamine has marked central stimulant effects, while the seemingly paradoxical antihypertensive action of alpha$_2$ agonists such as clonidine may be due to central effects that outweigh their effects in vascular smooth muscle.

The differing characteristics of the sympathomimetics mean that they are used in a wide range of disorders. Those with alpha$_1$-agonist effects are mainly used to increase the blood pressure in hypotensive disorders and in shock (p. 1279.3). Some alpha agonists, such as phenylephrine (p. 1672.2), are also applied topically to produce vasoconstriction of mucosal surfaces and are used for the symptomatic relief of nasal congestion and in eye disorders; they may also be used as mydriatics. Alpha$_2$ agonists are used as central antihypertensives (see Clonidine, p. 1339.1), or in the treatment of glaucoma (see Apraclonidine, p. 2003.3). Beta$_1$ agonists are mainly used for their inotropic actions in acute heart failure and shock, while beta$_2$ agonists such as salbutamol (p. 1220.2) are used for their bronchodilator effects and as uterine relaxants in premature labour. Sympathomimetics with mainly CNS effects may be used as central stimulants (see Dexamfetamine, p. 2319.1).

Adverse Effects

Sympathomimetics may produce a wide range of adverse effects, generally resembling the effect of excessive stimulation of the sympathetic nervous system. These effects are mediated by the different types of adrenergic receptor, and the effects of individual drugs depend to a large extent on their relative activity at the different receptors, as well as the body's homoeostatic response. While many sympathomimetics are relatively selective for specific receptors, this depends on the dose, and at higher doses most have effects on all receptors.

Central effects may occur with all sympathomimetics and include anxiety, fear, restlessness, insomnia, confusion, irritability, headache, and psychotic states; dyspnoea, weakness, anorexia, nausea, and vomiting are also common. Although some sympathomimetics have direct effects, others do not cross the blood-brain barrier and their central effects appear to be a somatic response.

The most important adverse effects of the sympathomimetics are those that affect the cardiovascular system. Palpitations, tachycardia, and arrhythmias mainly result from stimulation of cardiac beta receptors, and there is also an increase in cardiac contractility; this may result in angina or cardiac arrest.

The effects on blood vessels depend on the relative effects at alpha and beta receptors, since most blood vessels have both. Stimulation of alpha receptors produces vasoconstriction, with resultant hypertension, and this may be severe enough to lead to cerebral haemorrhage or pulmonary oedema, particularly in overdosage. There may also be reflex bradycardia. Conversely, hypotension, with dizziness and fainting, and flushing, may occur due to beta$_2$-induced vasodilatation, and may contribute to tachycardia.

Alpha-mediated vasoconstriction causes cold extremities, since blood vessels supplying the skin and mucosa have only alpha receptors; this may lead to gangrene, particularly when sympathomimetics are infiltrated into digits. Extravasation similarly may cause tissue necrosis and sloughing. Topical application to mucosal surfaces also causes vasoconstriction, pain, and irritation; hypoxia may lead to rebound mucosal congestion.

Other effects include mydriasis, difficulty in micturition and urinary retention, piloerection, sweating, and increased salivation, all of which result from alpha$_1$ stimulation. Hypokalaemia and muscle tremor may occur as a result of beta$_2$ stimulation, although tremor may also occur as a somatic response. Effects on the uterus are complex and depend on the stage of the menstrual cycle; labour may be inhibited by beta$_2$ stimulation. Hyperglycaemia may occur due to complex metabolic effects, and lactic acidosis has also been reported.

Effects on the heart. The heart has mainly beta$_1$ adrenoceptors and cardiac arrhythmias are most likely with beta$_1$ agonists; increased mortality has been reported with the use of beta agonists in heart failure (see Ibopamine, p. 1407.2). A review[1] of vasopressor sympathomimetics, which are mainly used for their alpha-agonist properties, concluded that dopamine and adrenaline were associated with the highest risk, mainly of dose-related sinus tachycardia and ventricular arrhythmias. However, the clinical significance of most arrhythmias occurring with dopamine was considered questionable; supraventricular or ventricular arrhythmias with adrenaline were most likely in patients receiving general anaesthesia or with underlying disorders of cardiac conduction. The risk with noradrenaline was uncertain, though there are few clinical reports, while phenylephrine and methoxamine were thought unlikely to cause problems. Overall the frequency of serious problems with this class of drugs did not seem to be high, and benefits outweighed the risks in most patients.

Sympathomimetics may cause myocardial ischaemia, particularly in patients with ischaemic heart disease, and severe cardiovascular effects have occurred with the use of dobutamine for cardiac stress testing (see Diagnosis and Testing, p. 1366.2). In addition, myocardial infarction has been reported in an 11-year-old boy treated with nebulised racepinefrine for symptoms of croup,[2] and there have also been reports of myocardial ischaemia associated with adrenaline overdosage (see p. 1294.2).

1. Tisdale JE, *et al.* Proarrhythmic effects of intravenous vasopressors. *Ann Pharmacother* 1995; 29: 269–81.
2. Butte MJ, *et al.* Pediatric myocardial infarction after racemic epinephrine administration. Abstract: *Pediatrics* 1999; 104: 103–4. Full version: http://pediatrics.aappublications.org/cgi/content/full/104/1/e9 (accessed 07/10/05)

Topical use. Systemic effects may occasionally follow the local or topical use of sympathomimetics, for example as eye drops for the treatment of glaucoma.[1] Psychiatric effects including hallucinations and paranoia have also occurred after both proper and improper use of sympathomimetics in decongestant preparations.[2]

1. Everitt DE, Avorn J. Systemic effects of medications used to treat glaucoma. *Ann Intern Med* 1990; 112: 120–5.
2. Anonymous. Drugs that cause psychiatric symptoms. *Med Lett Drugs Ther* 1993; 35: 65–70.

Treatment of Adverse Effects

Most sympathomimetics have a short duration of action and treatment of adverse effects is mainly supportive; if given by infusion, stopping it or reducing the rate will be sufficient in many cases. A rapidly-acting alpha blocker, such as phentolamine, may be given to reverse alpha$_1$-mediated effects such as hypertension, while a beta blocker may be given for beta$_1$-mediated effects such as cardiac arrhythmias. In severe hypertension, rapidly-acting vasodilators such as glyceryl trinitrate have also been used.

In the case of extravasation of an alpha agonist, or injection into a digit, an alpha blocker such as phentolamine should be given as soon as possible to prevent tissue necrosis and ischaemic damage.

Non-catecholamine sympathomimetics may have a longer duration of action and adverse effects, particularly hypertension, may be prolonged.

Precautions

Sympathomimetics should be used with caution in patients with cardiovascular disorders, who may have an increased susceptibility to their effects. Particular care is needed in patients with cardiac arrhythmias, ischaemic heart disease, or hypertension. All sympathomimetics should generally be avoided in severe hypertension, although alpha agonists are particularly hazardous; they should also be used with caution in patients with occlusive vascular disease, who are at increased risk of peripheral ischaemia. Beta$_1$ agonists are a particular hazard in tachycardia. Sympathomimetics with beta$_2$ effects should be used with caution in obstructive cardiomyopathy and other disorders where a reduction in total peripheral resistance could be harmful.

Sympathomimetics should be avoided in phaeochromocytoma. Caution is also needed in patients with hyperthyroidism, who may be at increased risk of effects on the heart; elevated thyroid hormone concentrations may also enhance adrenoceptor sensitivity. Diabetics and elderly patients have a high incidence of atherosclerotic disease and may also be at higher risk; the effects of sympathomimetics on blood glucose should also be considered.

Alpha agonists in particular should be used with caution in angle-closure glaucoma, as well as in patients with prostate disorders, who may be at increased risk of urinary retention. Sympathomimetics with vasoconstrictor effects may reduce placental perfusion and should possibly be avoided in pregnancy; adrenaline and others with beta$_2$-mediated effects may also inhibit labour.

If sympathomimetics are used for circulatory support, hypovolaemia, metabolic acidosis, and hypoxia or hypercapnia should be corrected either before starting the sympathomimetic or while it is being given. Blood pressure should be monitored regularly during treatment.

Interactions

Interactions with sympathomimetics are complex and may be hazardous; they result mainly from their pharmacological actions at alpha and beta receptors.

Table 5. Actions of sympathomimetics.

	Action		Receptor specificity			
	Direct	Indirect	α	β_1	β_2	DA*
Adrenaline	+		+	+	+	
Dobutamine	+		+	+	+	
Dopamine	+	+	+	+		+
Dopexamine	+	+			+	+
Ephedrine	+	+	+	+	+	
Etilefrine	+		+	+	+	
Ibopamine		+	+	+	+	+
Isoprenaline	+			+	+	
Mephentermine	+	+	+	+		
Metaraminol	+	+	+	+		
Methoxamine	+		+			
Midodrine	+		+			
Noradrenaline	+		+	+		
Phenylephrine	+		+			

* = Dopaminergic

All cross-references refer to entries in Volume A

Increased cardiac effects may occur with drugs that increase the sensitivity of the myocardium to $beta_1$ agonists; hazardous arrhythmias may occur with volatile anaesthetics, particularly cyclopropane or halothane. Caution is also required with thyroid hormones, and with drugs that affect cardiac conduction, such as cardiac glycosides and antiarrhythmics.

All sympathomimetics affect blood pressure and should be used with caution with antihypertensive drugs or drugs that cause hypotension, particularly those whose action involves the sympathetic nervous system. Direct-acting sympathomimetics with alpha-agonist actions specifically reverse the hypotensive effect of adrenergic neurone blockers such as guanethidine, and severe hypertension may result. There are also complex interactions between both alpha and beta blockers and sympathomimetics, particularly those that have actions at both types of receptor. Alpha blockers antagonise the effects at alpha receptors but leave the beta-mediated effects unopposed, leading to an increased risk of hypotension and tachycardia. Beta blockers, especially those that are non-selective, antagonise the effects at beta receptors but leave the alpha-mediated effects unopposed, increasing the risk of hypertension and reflex bradycardia. They also antagonise the bronchodilating effects of $beta_2$ agonists. Severe anaphylaxis in patients taking non-cardioselective beta blockers may not respond to adrenaline (see below).

Hazardous interactions resulting in severe hypertension may occur with MAOIs (including RIMAs) and sympathomimetics, especially those that have indirect actions, since MAOIs increase the amount of noradrenaline stored in adrenergic nerve endings. Sympathomimetics for which the risk is particularly high include dexamfetamine, dopamine, dopexamine, ephedrine, isometheptene, mephentermine, metaraminol, methylphenidate, phentermine, phenylephrine, phenylpropanolamine, and pseudoephedrine. The effects of direct-acting sympathomimetics such as adrenaline and noradrenaline may also be slightly enhanced. For additional warnings see under Phenelzine (p. 445.1) and Moclobemide (p. 438.1).

Tricyclic antidepressants block the inactivation of adrenaline and noradrenaline by uptake into the nerve endings and may increase their effect; hypertension and arrhythmias may occur. Conversely, the effect of indirectly-acting sympathomimetics could theoretically be reduced by tricyclics, although there is little clinical evidence that this occurs. There is also no evidence that an interaction occurs when local anaesthetic solutions containing adrenaline or noradrenaline are used in patients taking MAOIs or tricyclics, although great care needs to be taken to avoid inadvertent intravenous injection of these local anaesthetic preparations.

Interactions may also occur between sympathomimetics and drugs that have similar or opposing effects through non-adrenergic mechanisms. Sympathomimetics with central actions may potentiate the effects of CNS stimulants, while the vasoconstrictor and pressor effects of alpha agonists may be enhanced by drugs with similar effects, such as ergot alkaloids or oxytocin. $Beta_2$-mediated hypokalaemia may be potentiated by other drugs that cause potassium loss, including corticosteroids, potassium-depleting diuretics, and aminophylline or theophylline; patients given high doses of $beta_2$ agonists with such drugs should have their plasma-potassium concentration monitored (see Interactions of Salbutamol, p. 1223.1). Hypokalaemia may also contribute to the increased susceptibility to cardiac arrhythmias caused by digoxin and other cardiac glycosides.

Antiparkinsonian drugs. Additive cardiovascular toxicity may occur when some sympathomimetics are given with antiparkinsonian drugs such as *levodopa* (see p. 908.1) and *bromocriptine* (see p. 899.1). Severe hypertension may also occur with some sympathomimetics and *selegiline* (see p. 916.2), possibly due to inhibition of peripheral monoamine oxidase.

Beta blockers. The interactions between beta blockers and sympathomimetics are complex and depend on the selectivity of both drugs. Patients given adrenaline (including the low doses used with local anaesthetics) while taking non-selective beta blockers such as *propranolol* can develop raised blood pressure due to alpha-mediated vasoconstriction, followed by reflex bradycardia, and occasionally cardiac arrest;[1] the bronchodilator effects of adrenaline and other $beta_2$ agonists are also inhibited. In contrast, cardioselective beta blockers such as *metoprolol*, have minimal effects on blood pressure and heart rate since they only inhibit the $beta_1$- mediated effects, leaving the $beta_2$-mediated vasodilatation to balance the vasoconstrictor effect. However, beta blockers that also have alpha-blocking effects, such as *carvedilol*, may cause hypotension since only the $beta_2$-induced vasodilatation remains; such an interaction has been reported with dobutamine.[2] Low doses of cardioselective beta blockers do not appear to interfere with sympathomimetic (isoprenaline)-induced bronchodilatation,[3] although the effect of larger doses is uncertain.

Propranolol has also been shown to inhibit the favourable pressor and bronchodilator responses to adrenaline when given for anaphylaxis.[4] Thus, patients on long-term treatment with some non-cardioselective beta blockers who develop anaphylaxis may be relatively refractory to adrenaline.

1. Jay GT, Chow MSS. Interaction of epinephrine and β -blockers. *JAMA* 1995; 274: 1830–2.
2. Lindenfeld J, *et al.* Hypotension with dobutamine: β -adrenergic antagonist selectivity at low doses of carvedilol. *Ann Pharmacother* 1999; 33: 1266–9.
3. Decalmer PBS, *et al.* Beta blockers and asthma. *Br Heart J* 1978; 40: 184–9.
4. Newman BR, Schultz LK. Epinephrine-resistant anaphylaxis in a patient taking propranolol hydrochloride. *Ann Allergy* 1981; 47: 35–7.

General anaesthetics. Anaesthesia may sensitise the myocardium to the effects of sympathomimetics, increasing the risk of arrhythmias, and fatalities have been attributed to the use of adrenaline with *halothane* anaesthesia.[1] It has been suggested[2] that the use of adrenaline for haemostasis during surgery is a particular risk, although use of a low dose may be safe in patients anaesthetised with *cyclopropane, halothane,* or similar volatile anaesthetics; other factors likely to increase the irritability of the myocardium, such as carbon-dioxide retention, hypoxia, or the use of cocaine, should be avoided.[2,3] For *halothane* or *trichloroethylene* anaesthesia a maximum strength for the adrenaline solution of 1 in 100 000, given at a rate not exceeding 10 mL in any 10-minute period or 30 mL in 1 hour, has been recommended;[3] this may also apply for cyclopropane, although the risk of arrhythmias is higher.[3] Other volatile anaesthetics generally appear to carry less risk.

1. Buzik SC. Fatal interaction? Halothane, epinephrine and tooth implant surgery. *Can Pharm J* 1990; 123: 68–9 and 81.
2. Anonymous. Anaesthetics and the heart. *Lancet* 1967; i: 484–5.
3. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. *Anesthesiology* 1968; 29: 763.

Theophylline. For discussion of possible interactions between sympathomimetics with beta-agonist actions and theophylline, see p. 1236.3.

Vasodilators. Paradoxical hypotension may occur when sympathomimetics with both alpha-and beta-agonist properties are given with *tolazoline,* and there has been a report[1] of fatal hypotension in a patient given tolazoline and dopamine together. The mechanism of the interaction appears to be antagonism of the alpha-mediated vasoconstrictor effect of the sympathomimetic by the alpha-blocking effects of tolazoline, leaving the vasodilator effects unopposed.

1. Carlon GC. Fatal association of tolazoline and dopamine. *Chest* 1979; 76: 336.

Talinolol *(rINN)* ⊗

Talinololum; Талинолол.

(±)-1-[*p*-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]-3-cyclohexylurea.

$C_{20}H_{33}N_3O_3$=363.5

CAS — 57460-41-0.

ATC — C07AB13.

ATC Vet — QC07AB13.

UNII — 3S822688KG.

Profile

Talinolol is a cardioselective beta blocker (p. 1316.3). It is given orally in the management of hypertension (p. 1251.1) and other cardiovascular disorders, in doses of up to 300 mg daily. It has also been given intravenously.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Cordanum; *Rus.*: Cordanum (Кордаум).

Teclothiazide Potassium *(BANM, rINNM)* ⊗

Kalii Teclothiazidum; Téclothiazide Potassique; Teclotiazida potásica; Tetrachlormethiazide Potassium; Калия Теклотиазид.

6-Chloro-3,4-dihydro-3-trichloromethyl-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide potassium.

$C_8H_7Cl_4N_3O_4S_2K$=454.2

CAS — 4267-05-4 (teclothiazide); 5306-80-9 (teclothiazide potassium).

UNII — SO5Y2RV80F.

Profile

Teclothiazide potassium is a thiazide diuretic (see Hydrochlorothiazide, p. 1403.2) used in the treatment of oedema.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Spain*: Quimodril.

Tedisamil *(BAN, USAN, rINN)*

KC-8857; Tédisamil; Tedisamilum; Тедизамил.

3',7'-Bis(cyclopropylmethyl)spiro[cyclopentane-1,9'-[3,7]diazabicyclo[3.3.1]nonane].

$C_{19}H_{32}N_2$=288.5

CAS — 90961-53-8.

ATC — C01BD06.

ATC Vet — QC01BD06.

UNII — A5VAY2U3R8.

Profile

Tedisamil is an antiarrhythmic under investigation for the treatment of atrial arrhythmias.

References.

1. Hohnloser SH, *et al.* Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol* 2004; 44: 99–104.
2. Krishnamoorthy S, Lip GY. Novel antiarrhythmic drugs in atrial fibrillation: focus on tedisamil. *Expert Opin Invest Drugs* 2009; 18: 1191–6.

Telmisartan *(BAN, USAN, rINN)*

BIBR 277; BIBR-277-SE; Telmisartaani; Telmisartán; Telmisartanum; Тельмизартан.

4'-[[4-Methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2-biphenylcarboxylic acid.

$C_{33}H_{30}N_4O_2$=514.6

CAS — 144701-48-4.

ATC — C09CA07.

ATC Vet — QC09CA07.

UNII — U5SYW473RQ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane. it dissolves in 1M sodium hydroxide. It exhibits polymorphism.

USP 36: (Telmisartan). A white or slightly yellowish, crystalline powder. Practically insoluble in water; slightly soluble in methyl alcohol; sparingly soluble in dichloromethane; it dissolves in 1M sodium hydroxide. Store in airtight containers. Protect from light.

Uses and Administration

Telmisartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1) and for the prophylaxis of cardiovascular events in patients with certain risk factors (see Cardiovascular Risk Reduction, p. 1246.1).

Telmisartan is given orally. After a dose the hypotensive effect peaks within 3 hours and persists for at least 24 hours. The maximum hypotensive effect occurs within about 4 to 8 weeks after starting therapy.

In **hypertension**, telmisartan is given in an initial dose of 40 mg once daily. This may be adjusted, if necessary, within the range of 20 to 80 mg once daily. Low doses should be considered in patients with hepatic or renal impairment (see p. 1510.1).

For **cardiovascular risk reduction**, telmisartan may be given in a dose of 80 mg once daily.

The hydrochloride salt has also been used.

Reviews.

1. Sharpe M, *et al.* Telmisartan: a review of its use in hypertension. *Drugs* 2001; 61: 1501–29.
2. Battershill AJ, Scott LJ. Telmisartan: a review of its use in the management of hypertension. *Drugs* 2006; 66: 51–83.
3. Gosse P. A review of telmisartan in the treatment of hypertension: blood pressure control in the early morning hours. *Vasc Health Risk Manag* 2006; 2: 195–201.
4. Yamagishi S, *et al.* Potential utility of telmisartan, an angiotensin II type 1 receptor blocker with peroxisome proliferator-activated receptor-γ (PPAR-γ)-modulating activity for the treatment of cardiometabolic disorders. *Curr Mol Med* 2007; 7: 463–9.
5. Francischetti EA, *et al.* Treatment of hypertension in individuals with the cardiometabolic syndrome: role of an angiotensin II receptor blocker, telmisartan. *Expert Rev Cardiovasc Ther* 2008; 6: 289–303.
6. Rosario BH, Hendra TJ. Telmisartan in the treatment of hypertension. *Expert Opin Drug Metab Toxicol* 2008; 4: 485–92.
7. Xi GL, *et al.* Meta-analysis of randomized controlled trials comparing telmisartan with losartan in the treatment of patients with hypertension. *Am J Hypertens* 2008; 21: 546–52.
8. Baumhäkel M, Böhm M. Telmisartan prevents cardiovascular events in a broad group of at-risk patients. *Expert Opin Pharmacother* 2009; 10: 3113–17.

9. Burnier M. Telmisartan: a different angiotensin II receptor blocker protecting a different population? *J Int Med Res* 2009; 37: 1662–79.
10. Salzerano D, *et al.* New standards in hypertension and cardiovascular risk management: focus on telmisartan. *Vasc Health Risk Manag* 2010; 6: 113–33.
11. Zheng Z, *et al.* A systematic review and meta-analysis of telmisartan versus valsartan in the management of essential hypertension. *J Clin Hypertens (Greenwich)* 2010; 12: 414–21.

Administration in hepatic or renal impairment. Doses of telmisartan may need to be adjusted in patients with hepatic or renal impairment.

- Giving telmisartan to patients with *hepatic impairment* resulted in an increase in bioavailability and a reduction in clearance compared with healthy subjects.[1] Although telmisartan was well tolerated, it was suggested that lower doses should be considered. In the UK telmisartan is contra-indicated in severe hepatic impairment and a maximum dose of 40 mg once daily is recommended for patients with mild to moderate impairment.
- Telmisartan appears to be well tolerated in patients with *renal impairment*, including those on dialysis.[2] However, in the UK, an initial dose of 20 mg once daily is recommended for patients with severe renal impairment or on haemodialysis.

1. Stangier J, *et al.* Pharmacokinetics and safety of intravenous and oral telmisartan 20 mg and 120 mg in subjects with hepatic impairment compared with healthy volunteers. *J Clin Pharmacol* 2000; 40: 1355–64.
2. Sharma AM, *et al.* Telmisartan in patients with mild/moderate hypertension and chronic kidney disease. *Clin Nephrol* 2005; 63: 250–7.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1. Telmisartan should be used with caution in patients with hepatic impairment or biliary obstruction.

References.
1. Michel MC, *et al.* Safety of telmisartan in patients with arterial hypertension: an open-label observational study. *Drug Safety* 2004; 27: 335–44.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies telmisartan as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Digoxin. Telmisartan may increase serum concentrations of digoxin (see Angiotensin II Receptor Antagonists under Interactions of Digoxin, p. 1356.1) but the interaction is probably not clinically significant.

Pharmacokinetics

Telmisartan is rapidly absorbed from the gastrointestinal tract; the absolute oral bioavailability is dose-dependent and is about 42% after a 40-mg dose and 58% after a 160-mg dose. Peak plasma concentrations of telmisartan are reached about 0.5 to 1 hour after an oral dose. Telmisartan is over 99% bound to plasma proteins. It is excreted almost entirely in the faeces via bile, mainly as unchanged drug. The terminal elimination half-life of telmisartan is about 24 hours.

References.
1. Stangier J, *et al.* Absorption, metabolism, and excretion of intravenously and orally administered [^{14}C]telmisartan in healthy volunteers. *J Clin Pharmacol* 2000; 40: 1312–22.
2. Deppe S, *et al.* Telmisartan: a review of its pharmacodynamic and pharmacokinetic properties. *Expert Opin Drug Metab Toxicol* 2010; 6: 863–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Deprevex; Gliosartan; Micardis; *Austral.*: Micardis; *Austria*: Micardis; *Belg.*: Kinzalmono; Micardis; *Braz.*: Micardis; Pritor; *Canad.*: Micardis; *Chile*: Cordiax; Micardis; Samertan†; *China*: An Ya (安亚); An Yi Ning (安怡宁); Bang Tan (邦坦); Bei Di Ning (倍迪宁); Bo Xin Shu (博欣舒); Chang Ping (常平); Da Shu Ya (达舒亚); Di Sai Ping (迪赛平); Di Yi Ning (蒂益宁); Fan Tan (凡坦); Heng Bei (恒贝); Heng Xue Su (恒雪素); Huo Ping (获平); Jia Se Yi (嘉瑟宜); Kang Chu (康楚); Li Lai Ke (利来客); Li Wen (立文); Long Shu Ya (隆舒雅); Luo Ge Le (洛格乐); Luo Sha Ning (洛莎宁); Mei Si (美斯); Micardis (美卡素); Nideshu (尼德舒); Nuo Jin Ping (诺金平); Nuo Shi Mei (诺适美); Ou Mei Ning (欧美宁); Ping Ke Ya Xin (平克亚欣); Pu Mei Te (浦美特); Qu Ya (曲亚); Sai Ka (赛卡); Saitan (赛坦); Sha Tai Qi (沙泰齐); Sha Ting Ning (沙汀宁); Shang Er Ning (尚尔宁); Shi Ji (施吉); Shu Luo Ning (舒洛宁); Si Tai Le (斯泰乐); Sonia (舒尼亚); Su Ding (素定); Tan Xin Suo (坦芯素); Te Li Kang (特立康); Ti Yu (提愈); Tian He Heng (天禾恒); TianYi (天易); Xin Rui (欣蕊); Xin Yi Er (欣益尔); Xue Ying Ping (雪盈平); Ya Ping (雅屏); Ya Tan (亚坦); Yaweiyi (亚维伊); Yi Ya Ping (益亚平); Yu Le Ning (毓乐宁); Zhi Xin Feng (至信风); *Cz.*: Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Tezeo; Tolura; Zanacodar; *Denm.*: Micardis; Pritor†; *Fin.*: Kinzalmono; Micardis; *Fr.*: Micardis; Pritor; *Ger.*: Kinzalmono; Micardis; *Gr.*: Micardis; Pritor; *Hong Kong*: Micardis; *Hung.*: Micardis; Pritor; *India*: Anzitel; Arbitel; Cortel; Cresar; Etela; Hytel; Lovetel; Mistra; Mytel; Newtel; Oditel; Telma; Telpres; *Indon.*: Micardis; *Irl.*: Actelsar; Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Telma; Tolura; Zanacodar; *Israel*: Micardis†; *Ital.*: Micardis; Pritor; *Jpn*: Micardis; *Malaysia*: Micardis; *Mex.*: Micardis; Predxal; *Neth.*: Dinortes; Kinzalmono; Micardis; Mirpresoc; Pritor; Telma; Tolura; Zanacodar; *Norw.*: Micardis; *NZ*: Micardis†; *Philipp.*: Micardis; Pritor; *Pol.*: Kinzalmono; Micardis; Pritor; Tolura; *Port.*: Kinzalmono; Micardis; Pritor; *Rus.*: Micardis (Микардис); Pritor (Прайтор); *S. Afr.*: Micardis; Pritor; *Singapore*: Micardis; *Spain*: Micardis; Pritor; *Swed.*: Micardis; *Switz.*: Kinzal; Micardis; *Thai.*: Micardis; *Turk.*: Micardis; Pritor; *UK*: Micardis; *Ukr.*: Micardis (Микардис); Pritor (Прайтор); *USA*: Micardis; *Venez.*: Micardis; Pritor.

Multi-ingredient Preparations. *Arg.*: Gliosartan Plus; Micardis Amlo; Micardis Plus; *Austral.*: Micardis Plus; Twynsta; *Austria*: MicardisPlus; *Belg.*: Kinzalkomb; Micardis Plus; Twynsta; *Braz.*: Micardis Anlo; Micardis HCT; Pritor HCT†; *Canad.*: Micardis Plus; Twynsta; *Chile*: Cordiax D; Micardis Plus; *China*: Micardis Plus (美嘉素); *Cz.*: Kinzalkomb; MicardisPlus; PritorPlus; Twynsta; *Denm.*: MicardisPlus; PritorPlus; *Fin.*: Kinzalkomb; MicardisPlus; *Fr.*: MicardisPlus; PritorPlus; Twynsta; *Ger.*: Kinzalkomb; MicardisPlus; Twynsta; *Gr.*: Micardis Plus; Pritor Plus; Twynsta; *Hong Kong*: Micardis Plus; *Hung.*: MicardisPlus; PritorPlus; *India*: Anzitel-H; Arbitel-H; Cortel-A; Cortel-H; Etela-H; Hytel-H; Lovetel-H; Mytel-H; Newtel-H; Oditel-H; Telma-H; Telpres-H; *Indon.*: Micardis Plus; *Irl.*: Kinzalkomb; MicardisPlus; Onduarp; PritorPlus; Twynsta; *Ital.*: Micardis Plus; PritorPlus; *Malaysia*: Micardis Plus; *Mex.*: Micardis Plus; Predxal Plus; *Neth.*: Kinzalkomb; Micardis Plus; Onduarp; PritorPlus; Tardipan; Twynsta; *Norw.*: MicardisPlus; *Philipp.*: Micardis Plus; PritorPlus; *Pol.*: Kinzalkomb; Micardis Plus; Pritor Plus; Twynsta; *Port.*: Kinzalkomb; Micardis Plus; PritorPlus; Twynsta; *Rus.*: MicardisPlus (МикардисПлюс); *S.Afr.*: Co-Micardis; *Singapore*: Micardis Plus; Twynsta; *Spain*: Micardis Plus; Pritor Plus; Twynsta; *Swed.*: Micardis Plus; *Switz.*: Kinzalplus; Micardis Amlo; MicardisPlus; *Thai.*: Micardis Plus; Twynsta; *Turk.*: Micardis Plus; Pritor Plus; *UK*: MicardisPlus; *Ukr.*: MicardisPlus (МикардисПлюс); *USA*: Micardis HCT; *Venez.*: Micardis Plus; Pritor Plus.

Pharmacopoeial Preparations
USP 36: Telmisartan and Hydrochlorothiazide Tablets; Telmisartan Tablets.

Temocapril Hydrochloride *(BANM, USAN, rINNM)*

CS-622; Hidrocloruro de temocapril; Témocapril, Chlorhydrate de; Temocapril, hidrocloruro de; Temocaprili Hydrochloridum; Темокаприла Гидрохлорид.

(+)-(2*S*,6*R*)-6-[[(1*S*)-1-Ethoxycarbonyl-3-phenylpropyl]amino] tetrahydro-5-oxo-2-(2-thienyl)-1,4-thiazepine-4(5*H*)-acetic acid hydrochloride.

$C_{23}H_{28}N_2O_5S_2$,HCl=513.1

CAS — 111902-57-9 (temocapril); 110221-44-8 (temocapril hydrochloride).

ATC — C09AA14.

ATC Vet — QC09AA14.

UNII — 8G820195VP.

Profile

Temocapril is an ACE inhibitor (p. 1282.2) that has been used in the treatment of hypertension (p. 1251.1). It owes its activity to the diacid temocaprilat to which it is converted after oral doses.

References.
1. Nakashima M, *et al.* Pharmacokinetics of temocapril hydrochloride, a novel angiotensin converting enzyme inhibitor, in renal insufficiency. *Eur J Clin Pharmacol* 1992; 43: 657–9.
2. Oguchi H, *et al.* Pharmacokinetics of temocapril and enalapril in patients with various degrees of renal insufficiency. *Clin Pharmacokinet* 1993; 24: 421–7.
3. Furuta S, *et al.* Pharmacokinetics of temocapril, an ACE inhibitor with preferential biliary excretion, in patients with impaired liver function. *Eur J Clin Pharmacol* 1993; 44: 383–5.
4. Arakawa M, *et al.* Pharmacokinetics and pharmacodynamics of temocapril during repeated dosing in elderly hypertensive patients. *Eur J Clin Pharmacol* 2001; 56: 775–9.
5. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet* 2002; 41: 207–24.
6. Yasunari K, *et al.* Pharmacological and clinical studies with temocapril, an angiotensin converting enzyme inhibitor that is excreted in the bile. *Cardiovasc Drug Rev* 2004; 22: 189–98.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Acecol.

Tenecteplase *(BAN, USAN, rINN)*

Tenecteplasa; Ténectéplase; Tenecteplasum; TNK-tPA; Тенектеплаз.

[103-L-Asparagine-117-L-glutamine-296-L-alanine-297-L-alanine-298-L-alanine-299-L-alanine]plasminogen activator (human tissue-type).

CAS — 191588-94-0.

ATC — B01AD11.

ATC Vet — QB01AD11.

UNII — WGD229O42W.

Description. Tenecteplase is a 527 amino acid glycoprotein produced by recombinant DNA technology. It is a modified form of human tissue plasminogen activator.

Uses and Administration

Tenecteplase is a thrombolytic drug. It converts plasminogen to its active form plasmin, resulting in fibrinolysis and dissolution of blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on p. 1124.3. Tenecteplase is a fibrin-specific thrombolytic (see p. 1245.3).

Tenecteplase is used similarly to streptokinase (p. 1503.1) in acute myocardial infarction (p. 1257.1). It is given intravenously as a single bolus dose over 5 to 10 seconds as soon as possible after the onset of symptoms. The dose is based on body-weight and ranges from 30 mg in patients less than 60 kg to a maximum of 50 mg in those 90 kg or above.

References.
1. Cannon CP, *et al.* TNK-tissue plasminogen activator compared with front-loaded alteplase in acute myocardial infarction: results of the TIMI 10B trial. *Circulation* 1998; 98: 2805–14.
2. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet* 1999; 354: 716–22.
3. The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet* 2001; 358: 605–13.
4. Meizer C, *et al.* Fibrinolysis of acute peripheral arterial occlusion with tenecteplase—a new weight-optimized treatment regimen. *J Thromb Thrombolysis* 2004; 18: 43–6.
5. Spöhr F, *et al.* International multicentre trial protocol to assess the efficacy and safety of tenecteplase during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest: the Thrombolysis in Cardiac Arrest (TROICA) Study. *Eur J Clin Invest* 2005; 35: 315–23.
6. Kelly RV, *et al.* Safety of adjunctive intracoronary thrombolytic therapy during complex percutaneous coronary intervention: initial experience with intracoronary tenecteplase. *Catheter Cardiovasc Interv* 2005; 66: 327–32.
7. Assessment of the Safety and Efficacy of a New Treatment Strategy with Percutaneous Coronary Intervention (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet* 2006; 367: 569–78.
8. Hull JE, *et al.* Tenecteplase in acute lower-leg ischemia: efficacy, dose, and adverse events. *J Vasc Interv Radiol* 2006; 17: 629–36.
9. Kline JA, *et al.* Tenecteplase to treat pulmonary embolism in the emergency department. *J Thromb Thrombolysis* 2007; 23: 101–5.
10. Johnson KK, *et al.* Tenecteplase for malignant pericardial effusion. *Pharmacotherapy* 2007; 27: 303–5.
11. Melandri G, *et al.* Review of tenecteplase (TNKase) in the treatment of acute myocardial infarction. *Vasc Health Risk Manag* 2009; 5: 249–56.
12. Becattini C, *et al.* TIPES Study Group. Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. *Thromb Res* 2010; 125: e82–e86.
13. Tumlin J, *et al.* A phase III, randomized, double-blind, placebo-controlled study of tenecteplase for improvement of hemodialysis catheter function: TROPICS 3. *Clin J Am Soc Nephrol* 2010; 5: 631–6.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tenecteplase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

As for Streptokinase, p. 1507.1

Pharmacokinetics

After intravenous injection in patients with acute myocardial infarction, tenecteplase has a biphasic clearance from plasma with an initial half-life of 20 to 24 minutes and a terminal phase half-life of 90 to 130 minutes. It is cleared mainly by hepatic metabolism.

Reviews.
1. Tanswell P, *et al.* Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet* 2002; 41: 1229–45.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Metalyse; *Austria*: Metalyse; *Belg.*: Metalyse; *Braz.*: Metalyse; *Canad.*: TNKase; *Chile*: Metalyse; *Cz.*: Metalyse; *Denm.*: Metalyse; *Fin.*: Meta-

lyse; *Fr.*: Metalyse; *Ger.*: Metalyse; *Gr.*: Metalyse; *Hong Kong*: Metalyse; *Hung.*: Metalyse; *Irl.*: Metalyse; *Ital.*: Metalyse; *Malaysia*: Metalyse; *Mex.*: Metalyse; *Neth.*: Metalyse; *Norw.*: Metalyse; *NZ*: Metalyse; *Pol.*: Metalyse; *Port.*: Metalyse; *Rus.*: Metalyse (Метализе); *S.Afr.*: Metalyse; *Singapore*: Metalyse; *Spain*: Metalyse; *Swed.*: Metalyse; *Switz.*: Metalyse; *Thai.*: Metalyse; *Turk.*: Metalyse; *UK*: Metalyse; *Ukr.*: Metalize (Метализе); *USA*: TNKase.

Terazosin Hydrochloride

(BANM, USAN, rINNM)

Abbott-45975; Hidrocloruro de terazosina; Teratsosiliny-drokloridi; Terazosin Hidroklorür; Terazosina, hidrocloruro de; Térazosine, chlorhydrate de; Terazosinhydrokloríd; Terazosini Hydrochloridum; Теразозина Гидрохлорид.

1-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-4-(tetrahydro-2-furoyl)piperazine hydrochloride dihydrate; 6,7-Dimethoxy-2-(4-(tetrahydrofuran-2-carbonyl)piperazin-1-yl)quinazolin-4-ylamine hydrochloride dihydrate.

$C_{19}H_{25}N_5O_4.HCl.2H_2O$=459.9

CAS — 63590-64-7 (terazosin); 63074-08-8 (anhydrous terazosin hydrochloride); 70024-40-7 (terazosin hydrochloride dihydrate).

ATC — G04CA03.

ATC Vet — QG04CA03.

UNII — D32S14F082 (terazosin hydrochloride); 8QOP8Z9955 (anhydrous terazosin hydrochloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Terazosin Hydrochloride Dihydrate). White or slightly yellow, crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol; practically insoluble in acetone. A 2% solution in water has a pH of 3.0 to 5.0. Protect from light.

USP 36: (Terazosin Hydrochloride). A white to pale yellow, crystalline powder, soluble in water and in methyl alcohol; freely soluble in isotonic saline solution; slightly soluble in alcohol and in 0.1N hydrochloric acid; practically insoluble in acetone and in hexanes; very slightly soluble in chloroform. Store in airtight containers at a temperature between 20 degrees and 25 degrees.

Uses and Administration

Terazosin is an alpha$_1$-adrenoceptor blocker (p. 1243.1) with actions similar to those of prazosin (p. 1474.1), but a longer duration of action.

It is used in the management of hypertension (p. 1251.1) and in benign prostatic hyperplasia (p. 2347.1) to relieve symptoms of urinary obstruction.

Terazosin is given orally as the hydrochloride, but doses are usually expressed in terms of the base. Terazosin hydrochloride 1.2 mg is equivalent to about 1 mg of terazosin. After oral doses its hypotensive effects are seen within 15 minutes and may last for up to 24 hours, permitting once daily dosage.

To avoid the risk of collapse which may occur in some patients after the first dose the initial dose for both hypertension and benign prostatic hyperplasia is 1 mg of terazosin at bedtime, increasing gradually at intervals of 7 days according to the patient's response. For **hypertension** the usual maintenance dose is 2 to 10 mg once daily and the usual maximum dose is 20 mg daily in a single dose or two divided doses. For **benign prostatic hyperplasia** the usual maintenance dose is 5 to 10 mg once daily.

Reviews.

1. Titmarsh S, Monk JP. Terazosin: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in essential hypertension. *Drugs* 1987; 33: 461–77.
2. Achari R, Laddu A. Terazosin: a new alpha adrenoceptor blocking drug. *J Clin Pharmacol* 1992; 32: 520–3.
3. Wilt TJ, *et al.* Terazosin for benign prostatic hyperplasia. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 01/02/06).

Adverse Effects, Treatment, and Precautions

As for Prazosin Hydrochloride, p. 1474.3.

Overdosage. A report of sinus bradycardia and hypotension associated with ingestion of 300 mg of terazosin with suicidal intent.[1] The patient recovered with no sequelae after supportive treatment with atropine and intravenous fluids.

1. Seak C-J, Lin C-C. Acute intoxication with terazosin. *Am J Emerg Med* 2008; 26: 117.e5–117.e6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies terazosin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Urinary incontinence. For reference to urinary incontinence associated with terazosin, see under Adverse Effects of Prazosin Hydrochloride, p. 1475.1.

Interactions

As for Prazosin Hydrochloride, p. 1475.1.

Pharmacokinetics

Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses; the bioavailability is reported to be about 90%. Peak plasma concentrations are achieved in about 1 hour. Terazosin is 90 to 94% protein bound. It is metabolised in the liver; one of the metabolites is reported to possess antihypertensive activity. The half-life in plasma is about 12 hours. Terazosin is excreted in faeces via the bile, and in the urine, as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Andrin; Benaprost; Blavin; Eglidon; Flumarc; Fosfomik; Geriprost; Isontyn; Panaprost; Proxatan; Rotiaz†; Teril; *Austral.*: Hytrin; *Austria*: Urocard; Uroflo; Vicard; *Belg.*: Hytrin; Terazosabb; Uro-Hytrin†; *Braz.*: Hytrin; *Canad.*: Hytrin; *Chile*: Adecur; Hytrin; *China*: Hytrin (高特灵); Jun Yi (均益); Ke Pai (可派); Luo Di Er (罗迪尔); Mei Li Chang (美派畅); Ou De Man (欧得曼); Pai Su (派速); Shi Ai Te (施艾特); Tai Le (泰乐); Yue Ke (悦克); Zheng Shu (正舒); *Cz.*: Hytrin; Kornam; *Denm.*: Sinalfa; *Fr.*: Dysalfa; Hytrine; *Ger.*: Flotrin; Heitrin; Tera; Terablock; Teranar; Terazid†; Terazoflo†; *Gr.*: Hytrin; Vlanodrin; *Hong Kong*: Hytrin; *Hung.*: Hytrin; Setegis; *India*: Gotera; Hytrin; Olyster; Zytrin; *Indon.*: Hytrin; *Irl.*: Benph; Hytrin; *Israel*: Hytrin; *Ital.*: Extersin; Ezosina; Itrin; Prostatil; Terafluss; Teraprost; Unoprost; Urodie; *Malaysia*: Conmy; Hytrin; Ralsin; Terasin; *Mex.*: Adecur; Hytrin; Romaken; *Neth.*: Hytrin; *Norw.*: Sinalfa; *NZ*: Hytrin; *Philipp.*: Conmy; Hykor; Hytrin; Hyzin; Lotencin; *Pol.*: Hytrin; Kornam; Setegis; Tesin†; *Port.*: Hytrin; *Rus.*: Kornam (Корнам); Setegis (Сетегис); *S.Afr.*: Hytrin; *Singapore*: Hytrin; Terasin; *Spain*: Alfaprost; Deflox; Magnurol; Mayul; Sutif; Teraumon; Zayasel; *Swed.*: Hytrinex; Sinalfa; *Switz.*: Hytrin BPH; *Thai.*: Hytrin; *Turk.*: Hytrin; Teranar; Teraumon; Tezoteva; *UK*: Hytrin; *Ukr.*: Alfater (Альфатер); Kornam (Корнам)†; Setegis (Сетегис); *USA*: Hytrin; *Venez.*: Adecur; Hytrin.

Pharmacopoeial Preparations

USP 36: Terazosin Capsules; Terazosin Tablets.

Tertatolol Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tertatolol; S-2395 (tertatolol or tertatolol hydrochloride); SE-2395 (tertatolol or tertatolol hydrochloride); Tertatolol, Chlorhydrate de; Tertatolol, hidrocloruro de; Tertatolol Hydrochloridum; Тертатолола Гидрохлорид.

(±)-1-(*tert*-Butylamino)-3-(thiochroman-8-yloxy)propan-2-ol hydrochloride.

$C_{16}H_{25}NO_2S.HCl$=331.9

CAS — 34784-64-0 (tertatolol); 33580-30-2 (tertatolol hydrochloride).

ATC — C07AA16.

ATC Vet — QC07AA16.

Profile

Tertatolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic activity.

Tertatolol is given orally as the hydrochloride in the management of hypertension (p. 1251.1) in a dose of 5 mg tertatolol hydrochloride once daily, increased to 10 mg once daily if required.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Artex; *Gr.*: Artexal†; *Irl.*: Artexal†; *Neth.*: Artex; *Port.*: Artex.

Tezosentan *(BAN, rINN)*

Tezosentan; Tezosentan; Tezosentanum; Тезозентан.

N-(6-(2-Hydroxyethoxy)-5-(o-methoxyphenoxy)-2-[2-(1*H*-tetrazol-5-yl)-4-pyridyl]-4-pyrimidinyl)-5-isopropyl-2-pyridinesulfonamide.

$C_{27}H_{27}N_9O_6S$=605.6

CAS — 180384-57-0.

UNII — 64J9J55263.

Profile

Tezosentan is an endothelin receptor antagonist that has been studied in acute heart failure.

References.

1. Torre-Amione G, *et al.* Hemodynamic effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients with class III to IV congestive heart failure. *Circulation* 2001; 103: 973–80.
2. Tovar JM, Gums JG. Tezosentan in the treatment of acute heart failure. *Ann Pharmacother* 2003; 37: 1877–83.
3. Cotter G, *et al.* The hemodynamic and neurohormonal effects of low doses of tezosentan (an endothelin A/B receptor antagonist) in patients with acute heart failure. *Eur J Heart Fail* 2004; 6: 601–9.
4. McMurray JJV, *et al.* Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA* 2007; 298: 2009–19.

Tiadenol *(rINN)*

LL-T558; Tiadénol; Tiadenolum; Тиаденон.

2,2'-(Decamethylenedithio)diethanol.

$C_{14}H_{30}O_2S_2$=294.5

CAS — 6964-20-1.

ATC — C10AX03.

ATC Vet — QC10AX03.

UNII — 22251270CX.

Profile

Tiadenol is a lipid regulating drug used in the treatment of hyperlipidaemias (p. 1248.1). The usual oral dose is 1.6 to 2.4 g daily in divided doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mon.*: Fonlipol.

Ticagrelor *(BAN, USAN, rINN)*

AR-C126532XX; AZD-6140; Ticagrélor; Ticagrelorum; Тикагрелор.

(1*S*,2*S*,3*R*,5*S*)-3-(7-[[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol.

$C_{23}H_{28}F_2N_6O_4S$=522.6

CAS — 274693-27-5.

ATC — B01AC24.

ATC Vet — QB01AC24.

UNII — GLH0314RVC.

Uses and Administration

Ticagrelor is an adenosine triphosphate analogue and acts as a reversible purinoreceptor P2Y$_{12}$-antagonist in a similar manner to clopidogrel (p. 1342.3), inhibiting adenosine diphosphate-mediated platelet aggregation. It is given orally, usually with low-dose aspirin, for the prevention of thromboembolism in patients with acute coronary syndromes. A single loading dose of 180 mg is given, followed by a maintenance dose of 90 mg twice daily.

References.

1. Wallentin L, *et al.* PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; 361: 1045–57.
2. Anderson SD, *et al.* Efficacy and safety of ticagrelor: a reversible P2Y12 receptor antagonist. *Ann Pharmacother* 2010; 44: 524–37.
3. Gurbel PA, *et al.* Ticagrelor for the treatment of arterial thrombosis. *Expert Opin Pharmacother* 2010; 11: 2251–9.
4. Abergel E, Nikolsky E. Ticagrelor: an investigational oral antiplatelet treatment for reduction of major adverse cardiac events in patients with acute coronary syndrome. *Vasc Health Risk Manag* 2010; 6: 963–77.
5. Nawarskas JJ, Clark SM. Ticagrelor: a novel reversible oral antiplatelet agent. *Cardiol Rev* 2011; 19: 95–100.
6. James SK, *et al.* Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised PLATelet inhibition and patient Outcomes (PLATO) trial. *BMJ* 2011; 342: d3527.
7. NICE. Ticagrelor for the treatment of acute coronary syndromes (issued October 2011). Available at: http://www.nice.org.uk/guidance/TA236/Guidance/pdf (accessed 08/03/12)

Adverse Effects and Precautions

The most common adverse effect associated with the use of ticagrelor (as with other reversible purinoreceptor P2Y$_{12}$-antagonist) is bleeding disorders (see Effects on the Blood, under Adverse Effects and Precautions of Ticlopidine, p. 1512.3). Ticagrelor should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or condition with an increased risk of bleeding such as peptic ulcer disease, intracranial haemorrhage, or moderate to severe liver dysfunction. To avoid excessive bleeding, treatment with ticagrelor should be stopped 5 to 7 days before elective surgery. Treatment should not otherwise be prematurely stopped or interrupted; however, if this is necessary because of bleeding, ticagrelor should be restarted as soon as possible to avoid the risk of stent thrombosis, cardiovascular death, or myocardial infarction.

Mild to moderate dyspnoea, that often resolved without the need for treatment, was also commonly associated with

the use of ticagrelor. It should be used with caution in patients with a history of asthma or chronic obstructive pulmonary disease; no specific treatment is suggested for those who develop new, prolonged, or worsened dyspnoea, however, if dyspnoea is not tolerated UK licensed product information recommends that treatment with ticagrelor be stopped.

Asymptomatic ventricular pauses have been reported from early clinical studies and ticagrelor should be used with caution in patients with an increased risk of bradycardic events and in those taking drugs known to induce bradycardia (see below).

Serum creatinine levels may increase during treatment with ticagrelor; renal function should be checked one month after starting treatment and thereafter at appropriate intervals. Serum uric acid levels may also increase and ticagrelor should be used with caution in patients with a history of hyperuricaemia or gouty arthritis; use in uric acid nephropathy is not recommended.

References.
1. Gaglia MA, Waksman R. Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding ticagrelor. *Circulation* 2011; 123: 451–6.

Interactions

Ticagrelor is mainly metabolised by cytochrome P450 isoenzyme CYP3A4 and to a lesser extent by CYP3A5. The use of both strong inhibitors and inducers of CYP3A should therefore be avoided at the same time as ticagrelor use. Ticagrelor, itself, is a mild inhibitor of CYP3A4 and as such should not be given with CYP3A4 substrates that have a narrow therapeutic index, such as cisapride or ergot alkaloids. It also inhibits the p-glycoprotein transporter system and thus digoxin and ciclosporin levels should be monitored if starting or changing ticagrelor therapy.

UK product information advises caution in the use of ticagrelor with drugs known to cause bradycardia, such as beta blockers, calcium-channel blockers, and digoxin. Additionally, caution is needed when used with drugs known to alter haemostasis. Due to reports of cutaneous bleeding with SSRIs, caution is advised when giving these antidepressants with ticagrelor.

Pharmacokinetics

Ticagrelor is rapidly absorbed from the gastrointestinal tract with a mean absolute bioavailability of about 36%. Both ticagrelor and its active metabolite are extensively bound to plasma proteins (> 99.7%). The systemic exposure to the active metabolite is about 30 to 40% of the exposure to ticagrelor. The steady state volume of distribution for ticagrelor is about 88 litres and the mean half-life is about 7 hours for ticagrelor and 8.5 to 9 hours for the active metabolite. Ticagrelor is mainly metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and, to a lesser extent, CYP3A5. The primary route of elimination of the major metabolite of ticagrelor is likely to be biliary secretion. Recovery of ticagrelor and its major metabolite in the urine were less than 1% of the dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Brilique; *Braz.*: Brilinta; *Denm.*: Brilique; *Fr.*: Brilique; *Ger.*: Brilique; *Gr.*: Brilique; *Irl.*: Brilique; Possia; *Israel*: Brilinta; *Neth.*: Brilique; *Norw.*: Brilique; *Pol.*: Brilique; Possia; *Port.*: Brilique; Possia; *Singapore*: Brilinta; *Spain*: Brilique; *Swed.*: Brilique; *Switz.*: Brilique; *Thai.*: Brilinta; *UK*: Brilique; *USA*: Brilinta.

Ticlopidine Hydrochloride

(BANM, USAN, rINNM)

53-32C; 4-C-32; Hidrocloruro de ticlopidina; Ticlopidina, hidrocloruro de Ticlopidine, Chlorhydrate de; Ticlopidinhydrochlorid; Ticlopidini Hydrochloridum; Tiklopidiinihydroklorid; Tiklopidin hidroklorür; Tiklopidinhidroklorid; Tiklopidin-hydrochlorid; Tiklopidinhydroklorid; Tiklopidino hidrochloridas; Тиклопидина гидрохлорид

5-(2-Chlorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride.

$C_{14}H_{14}ClNS,HCl$=300.2

CAS — 55142-85-3 (ticlopidine); 53885-35-1 (ticlopidine hydrochloride).

ATC — B01AC05.

ATC Vet — QB01AC05.

UNII — ATL4914FMF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in dehydrated alcohol; very slightly soluble in ethyl acetate. A 2.5% solution in water has a pH of 3.5 to 4.0.

USP 36: (Ticlopidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in alcohol; very slightly soluble in ethyl acetate. Store in airtight containers at a temperature below 30 degrees.

Uses and Administration

Ticlopidine hydrochloride is a thienopyridine antiplatelet drug used in thromboembolic disorders (p. 1273.2). It is a platelet $P2Y_{12}$-receptor antagonist that acts by inhibiting adenosine diphosphate-mediated platelet aggregation. It may be given prophylactically as an alternative to aspirin in patients at risk of thrombotic stroke (p. 1269.2) and in the management of intermittent claudication (see Chronic Occlusive Peripheral Arterial Disease, p. 1272.3) and ischaemic heart disease. It is also licensed as an adjunct to aspirin for the prevention of subacute stent occlusion after intracoronary stenting (but see Reperfusion and Revascularisation Procedures, below). Ticlopidine may also be used to prevent occlusion and platelet loss during extracorporeal circulatory procedures.

In the prevention of thrombotic stroke, and in **intermittent claudication**, ticlopidine hydrochloride is given orally in a dose of 250 mg twice daily, with meals. For the prevention of subacute stent occlusion after **intracoronary stenting** ticlopidine hydrochloride is given in a dose of 250 mg twice daily for 4 weeks, starting at the time of stent placement.

Regular haematological monitoring is required during ticlopidine therapy (see Adverse Effects and Precautions, below).

References.
1. McTavish D, *et al.* Ticlopidine: an updated review of its pharmacology and therapeutic use in platelet-dependent disorders. *Drugs* 1990; 40: 238–59.
2. Flores-Runk P, Raasch RH. Ticlopidine and antiplatelet therapy. *Ann Pharmacother* 1993; 27: 1090–8.
3. Sharis PJ, *et al.* The antiplatelet effects of ticlopidine and clopidogrel. *Ann Intern Med* 1998; 129: 394–405.
4. Wallentin L. $P2Y_{12}$ inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. *Eur Heart J* 2009; 30: 1964–77.

Reperfusion and revascularisation procedures. Coronary stents are widely used as an adjunct to angioplasty to prevent acute vessel closure and to reduce restenosis (see Reperfusion and Revascularisation Procedures, p. 1259.2). Subacute thrombosis is a major complication of their use and patients were initially treated with an aggressive combination of anticoagulants and antiplatelets. However, it is now generally recognised that antiplatelet drugs alone are adequate in most patients.

Early studies[1-4] found that ticlopidine for 4 to 6 weeks after stenting, given with long-term aspirin, was at least as effective as an oral anticoagulant with aspirin, with some studies showing benefit in terms of thrombosis[1,4] or bleeding complications.[1] However, the risk of neutropenia limits the use of ticlopidine, and clopidogrel is now generally preferred, although there is some evidence[5] that shorter courses of ticlopidine (2 weeks) may be acceptable.

Ticlopidine has also been reported[6] to improve the long-term patency of saphenous vein bypass grafts used to treat peripheral vascular disease in the legs.

1. Schömig A, *et al.* A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. *N Engl J Med* 1996; 334: 1084–9.
2. Kastrati A, *et al.* Restenosis after coronary stent placement and randomization to a 4-week combined antiplatelet or anticoagulant therapy: six-month angiographic follow-up of the Intracoronary Stenting and Antithrombotic Regimen (ISAR) trial. *Circulation* 1997; 96: 462–7.
3. Bertrand ME, *et al.* Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the Full Anticoagulation versus Aspirin and Ticlopidine (FANTASTIC) study. *Circulation* 1998; 98: 1597–1603.
4. Leon MB, *et al.* A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998; 339: 1665–71.
5. Berger PB, *et al.* Safety and efficacy of ticlopidine for only 2 weeks after successful intracoronary stent placement. *Circulation* 1999; 99: 248–53.
6. Becquemin J-P. Effect of ticlopidine on the long-term patency of saphenous-vein bypass grafts in the legs. *N Engl J Med* 1997; 337: 1726–31.

Adverse Effects and Precautions

Bleeding is the most commonly reported adverse effect with thienopyridines; skin rashes may also occur, and gastrointestinal disturbances are common with ticlopidine. Blood dyscrasias, including neutropenia, thrombotic thrombocytopenic purpura, and aplastic anaemia, have occurred. There have been reports of hepatitis and cholestatic jaundice. Blood-lipid concentrations may increase during long-term therapy.

Ticlopidine and other thienopyridines should not be given to patients with haematopoietic disorders such as neutropenia or thrombocytopenia, haemorrhagic diathesis or other haemorrhagic disorders associated with a prolonged bleeding time, or conditions with an increased risk of bleeding such as peptic ulcer disease, acute cerebral haemorrhage, or severe liver dysfunction. Full blood counts should be performed before starting treatment with ticlopidine and every 2 weeks during the first 3 months of therapy. If ticlopidine is stopped during this period, a full blood count should be performed within 2 weeks of stopping treatment. Consideration should be given to stopping ticlopidine therapy 10 to 14 days before elective surgery.

Effects on the blood. Severe *neutropenia* or *agranulocytosis* may occur in about 1% of patients given ticlopidine[1] and fatal infection has been reported.[2] Neutropenia usually develops within the first 3 months of therapy and is reversible on stopping ticlopidine, but there has been a report[3] of a delayed reaction that occurred 18 days after ticlopidine was stopped. Isolated *thrombocytopenia* occurs in about 0.4% of patients and *thrombotic thrombocytopenic purpura* (TTP), sometimes fatal, has occurred.[1,4-8] The rate of TTP associated with ticlopidine use in patients with stents has been estimated at between 1 in 1600 and 1 in 5000.[8] Conversely, good results have been achieved with ticlopidine as a treatment for thrombotic thrombocytopenic purpura,[9,10] but it should only be used with extreme caution.[11] Aplastic anaemia has also occurred rarely with ticlopidine.[1,12]

Clopidogrel has also been associated with blood dyscrasias. Up to August 2004, the Australian Adverse Drug Reactions Advisory Committee (ADRAC)[13] had received 80 reports of blood dyscrasias associated with clopidogrel, although ticlopidine was associated with a much higher rate of reports. Individual cases of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome,[8,14-17] aplastic anaemia,[18] leucopenia,[19] and acquired haemophilia A,[20] have also been reported. However the most frequently reported adverse effect of clopidogrel, as with other antithrombotics such as prasugrel and ticagrelor, is bleeding, particularly when given with other drugs affecting coagulation; ADRAC had received 130 reports of haemorrhagic events, leading to fatalities in 18 cases following the use of clopidogrel.[13] The rate of major bleeding events with ticagrelor is similar to that with clopidogrel.[21]

1. Love BB, *et al.* Adverse haematological effects of ticlopidine: prevention, recognition and management. *Drug Safety* 1998; 19: 89–98.
2. Carlson JA, Maesner JE. Fatal neutropenia and thrombocytopenia associated with ticlopidine. *Ann Pharmacother* 1994; 28: 1236–8.
3. Parver DK, Hansen LA. Delayed neutropenia with ticlopidine. *Ann Pharmacother* 1994; 28: 1344–6.
4. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine: a review of 60 cases. *Ann Intern Med* 1998; 128: 541–4.
5. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura after stenting and ticlopidine. *Lancet* 1998; 352: 1036–7.
6. Steinhubl SR, *et al.* Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. *JAMA* 1999; 281: 806–10.
7. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with ticlopidine in the setting of coronary artery stents and stroke prevention. *Arch Intern Med* 1999; 159: 2524–8.
8. Zakarija A, *et al.* Ticlopidine- and clopidogrel-associated thrombotic thrombocytopenic purpura (TTP): review of clinical, laboratory, epidemiological, and pharmacovigilance findings (1989-2008). *Kidney Int* 2009; 75 (suppl 112s): S20–S24.
9. Vianelli N, *et al.* Thrombotic thrombocytopenic purpura and ticlopidine. *Lancet* 1991; 337: 1219.
10. Bobbio-Pallavicini E, *et al.* Antiplatelet agents in thrombotic thrombocytopenic purpura (TTP): results of a randomized multicenter trial by the Italian Cooperative Group for TTP. *Haematologica* 1997; 82: 429–35.
11. Rock G, *et al.* Thrombotic thrombocytopenic purpura treatment in year 2000. *Haematologica* 2000; 85: 410–19.
12. Symeonidis A, *et al.* Ticlopidine-induced aplastic anemia: two new case reports, review, and meta-analysis of 55 additional cases. *Am J Hematol* 2002; 71: 24–32.
13. Adverse Drug Reactions Advisory Committee (ADRAC). Clopidogrel—haemorrhage and haematological disorders. *Aust Adverse Drug React Bull* 2004; 23: 14–15. Also available at: http://www.tga.health.gov.au/adri/aadrb/aadr0408.htm (accessed 17/08/05)
14. Bennett CL, *et al.* Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med* 2000; 342: 1773–7.
15. Oomen PHN, *et al.* Hemolytic uremic syndrome in a patient treated with clopidogrel. *Ann Intern Med* 2000; 132: 1006.
16. Andersohn F, *et al.* Thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome associated with clopidogrel: report of two new cases. Abstract: *Heart* 2004; 90: e57. Full version: http://heart.bmjjournals.com/cgi/content/full/90/9/e57 (accessed 17/08/05)
17. von Mach M-A, *et al.* Subacute coronary stent thrombosis in a patient developing clopidogrel associated thrombotic thrombocytopenic purpura. Abstract: *Heart* 2005; 91: e14. Full version: http://heart.bmjjournals.com/cgi/content/full/91/2/e14 (accessed 17/08/05)
18. Trivier J-M, *et al.* Fatal aplastic anaemia associated with clopidogrel. *Lancet* 2001; 357: 446.
19. McCarthy MW, Kockler DR. Clopidogrel-associated leukopenia. *Ann Pharmacother* 2003; 37: 216–19.
20. Haj M, *et al.* Acquired haemophilia A may be associated with clopidogrel. *BMJ* 2004; 329: 323.
21. Gaglia MA, Waksman R. Overview of the 2010 Food and Drug Administration Cardiovascular and Renal Drugs Advisory Committee meeting regarding ticagrelor. *Circulation* 2011; 123: 451–6.

Effects on the gastrointestinal tract. Diarrhoea is a common adverse effect of ticlopidine therapy; it usually occurs during the first few months of therapy and resolves within 1 to 2 weeks without stopping therapy. However, there has been a report[1] of diarrhoea and weight loss of 2 months duration that first presented 2 years after ticlopi-

dine was started; diarrhoea resolved when ticlopidine was withdrawn.

1. Mansoor GA, Aziz K. Delayed chronic diarrhea and weight loss possibly due to ticlopidine therapy. *Ann Pharmacother* 1997; 31: 870–2.

Effects on the joints. Acute arthritis associated with a diffuse rash developed in a patient shortly after starting treatment with ticlopidine.[1] Both the rash and the arthritis resolved on withdrawal, and it was suggested that a hypersensitivity reaction might be involved. One case of polyarthritis and 3 cases of arthralgia associated with ticlopidine had been reported to the UK CSM up to March 2001. Two cases of acute arthritis have also been reported[2] with clopidogrel; symptoms developed 2 to 3 weeks after starting treatment and resolved after stopping.

1. Dakik HA, *et al.* Ticlopidine associated with acute arthritis. *BMJ* 2002; 324: 27.
2. Garg A, *et al.* Clopidogrel associated with acute arthritis. *BMJ* 2000; 320: 483.

Effects on the kidneys. A reversible deterioration in renal function has been reported in patients given ticlopidine after coronary stent implantation.[1,2] There has also been a report[3] of membranous nephropathy with nephrotic syndrome in a patient receiving clopidogrel.

1. Elsman P, Zijlstra F. Ticlopidine and renal function. *Lancet* 1996; 348: 273–4.
2. Virdee M, *et al.* Ticlopidine and renal function. *Lancet* 1996; 348: 1031–2.
3. Tholl U, *et al.* Clopidogrel and membranous nephropathy. *Lancet* 1999; 354: 1443–4.

Effects on the liver. Cholestatic hepatitis has been reported in patients receiving ticlopidine and is usually reversible when ticlopidine is stopped.[1-3] However, there have been reports of persistent cholestasis after ticlopidine withdrawal.[4,5] A case of granulomatous hepatitis has also been reported.[6] Clopidogrel was substituted for ticlopidine in a patient who had developed raised liver enzymes during ticlopidine treatment;[7] liver enzyme values returned to normal during continued clopidogrel therapy. However, there has been a report[8] of hepatotoxicity with clopidogrel.

1. Cassidy LJ, *et al.* Probable ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 1995; 29: 30–2.
2. Pérez-Balsa AM, *et al.* Hepatotoxicity due to ticlopidine. *Ann Pharmacother* 1998; 32: 1250–1.
3. Skurnik YD, *et al.* Ticlopidine-induced cholestatic hepatitis. *Ann Pharmacother* 2003; 37: 371–5.
4. Colivicchi F, *et al.* Ticlopidine-induced chronic cholestatic hepatitis: a case report. *Curr Ther Res* 1994; 55: 929–31.
5. Mambelli E, *et al.* Severe ticlopidine-induced cholestatic syndrome. *Blood Purif* 2007; 25: 441–5.
6. Ruiz-Valverde P, *et al.* Ticlopidine-induced granulomatous hepatitis. *Ann Pharmacother* 1995; 29: 633–4.
7. Zeolla MM, Carson JJ. Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity. *Ann Pharmacother* 1999; 33: 939–41.
8. Willens HJ. Clopidogrel-induced mixed hepatocellular and cholestatic liver injury. *Am J Ther* 2000; 7: 317–18.

Effects on the lungs. Bronchiolitis obliterans-organising pneumonia developed in a 76-year-old woman receiving ticlopidine and prednisone for temporal arteritis.[1] The condition resolved over several months when ticlopidine was withdrawn.

1. Alonso-Martinez JL, *et al.* Bronchiolitis obliterans-organizing pneumonia caused by ticlopidine. *Ann Intern Med* 1998; 129: 71–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ticlopidine as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Ticlopidine should be used with caution in patients receiving other drugs, such as anticoagulants and antiplatelet drugs, that increase the risk of bleeding. Ticlopidine is an inhibitor of cytochrome P450, including the isoenzymes CYP2C19, CYP2D6, and CYP2B6, and may inhibit the metabolism of other drugs that are metabolised by this route. The clearance of ticlopidine may be reduced by cimetidine. Corticosteroids may antagonise the effect of ticlopidine on bleeding time.

Anticoagulants. Use of ticlopidine with anticoagulants may increase the risk of bleeding. However, ticlopidine has been reported to antagonise the effect of *acenocoumarol* (see Antiplatelets under Interactions of Warfarin, p. 1532.3).

Antiepileptics. For a report of acute *phenytoin* toxicity in a well-stabilised patient following addition of ticlopidine, see p. 545.1.

Codergocrine. A study[1] in healthy subjects found that codergocrine mesilate reduced the plasma concentration of ticlopidine, probably by inhibiting its uptake from the gastrointestinal tract by organic anion transporting polypeptide (OATP)-B.

1. Lu W-J, *et al.* The effects of ergoloid mesylates and ginkgo biloba on the pharmacokinetics of ticlopidine. *J Clin Pharmacol* 2006; 46: 628–34.

Xanthines. For reference to the effect of ticlopidine on *theophylline* half-life and plasma clearance, see p. 1236.3.

Pharmacokinetics

Ticlopidine is rapidly and almost completely absorbed from the gastrointestinal tract. It is about 98% bound to plasma proteins. The terminal half-life during chronic dosing is reported to be about 30 to 50 hours. Ticlopidine is extensively metabolised in the liver. About 60% of a dose is excreted in the urine as metabolites and 25% in the faeces.

References.

1. Desager J-P. Clinical pharmacokinetics of ticlopidine. *Clin Pharmacokinet* 1994; 26: 347–55.
2. Buur T, *et al.* Pharmacokinetics and effect of ticlopidine on platelet aggregation in subjects with normal and impaired renal function. *J Clin Pharmacol* 1997; 37: 108–15.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dosier; Ticlid; Trombenal; *Austral.*: Ticlid†; Tilodene; *Austria*: Thrombodine; Tiklid; *Belg.*: Ticlid; *Braz.*: Desagreg; Plaketar; Plavasc; Ticlid; Ticlobal; *Chile*: Ateroclar; Plaquetil; Ticlid†; *China*: Ban Su (板苏); Bang Jie Qing (邦解清); Cisen (辰欣); LiDe (力得); Qi Luo (齐洛); Tailuda (泰禄达); Tian Xin Li Bo (天新利博); Ticlid (抵克立得); Yu Chuan Tong (玉川通); *Cz.*: Apo-Tic; Ipaton; Tagren; Ticlid†; *Fr.*: Ticlid; *Ger.*: Tiklyd; *Gr.*: Anghostan; Etfariol; Iriflexin; Labortina; Neo Pulvigal; Neo-omnipen; Ruxicolan; Ticlid; Ticlodone; *Hong Kong*: Aplaket; Ticlid; Tipidin; *Hung.*: Aclotin; Aplatic; Ipaton; Placor; Ticlid; Ticlogal; *India*: Aplaket; Ticlobest; Ticlop; Ticlopid; Tikleen; Tyklid; *Indon.*: Agulan; Cartrilet; Goclid; Nufaclapide; Piclodin; Platidine; Ticard; Ticlid; Ticlon; Ticlophar; Ticuring; *Ital.*: Antigreg; Aplaket; Chiaro; Clox; Fluilast; Flupid; Fluxidin; Klodin; Opteron; Ticlodone; Tiklid; *Jpn*: Panaldine; *Malaysia*: Antigreg; Aplaket; Strokan; Ticlid; Ticlopine†; Tipidin; *Mex.*: Ticlid†; *Norw.*: Ticlid; *Philipp.*: Clotidone†; Ticlid; Tikpid; Vasopid; *Pol.*: Aclotin; Apo-Clodin; Iclopid; Ifapidin; Ticlid; Ticlo; *Port.*: Aplaket; Beulife; Klodipin†; Movin; Plaquetal; Previta; Ticlodix; Ticlopat; Tiklyd; Tiropa; Trombopat; *Rus.*: Ticlid (Тиклид); Ticlo (Тикло); Tikleen (Тиклин)†; *Singapore*: Antigreg; Aplaket; Ticlid; Tiodin; Tipidin; *Spain*: Ticlodone; Tiklid; *Swed.*: Ticlid†; *Thai.*: Aplaket; Cenpidine; Siclot†; Ticlid; Ticlo; Ticlodin; Ticlopine; Tilopin; Tipidine; Viladil†; *Turk.*: Agretik; Ticlid; Ticlocard; *UAE*: Ticopar; *Ukr.*: Aclotin (Аклотин); Ipaton (Ипатон)†; *USA*: Ticlid; *Venez.*: Ticlid.

Multi-ingredient Preparations. *India*: Astic.

Pharmacopoeial Preparations

USP 36: Ticlopidine Hydrochloride Tablets.

Tilisolol Hydrochloride *(rINNM)* ⊗

Hidrocloruro de tilisolol; N-696; Tilisolol; Chlorhydrate de Tilisololi Hydrochloridum; Тилизолола Гидрохлорид.

(±)-4-[3-(tert-Butylamino)-2-hydroxypropoxy]-2-methylisocarbostyril hydrochloride.

$C_{17}H_{24}N_2O_3HCl$=340.8

CAS — 85136-71-6 (tilisolol); 62774-96-3 (tilisolol hydrochloride).

Profile

Tilisolol hydrochloride is a non-cardioselective beta blocker (p. 1316.3) with direct vasodilator activity. It is used in the management of angina pectoris (p. 1254.3) and hypertension (p. 1251.1) in oral doses of 10 to 20 mg once daily; up to a maximum of 30 mg once daily may be used if necessary.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Selecal.

Timolol Maleate *(BANM, USAN, rINNM)* ⊗

Maleato de timolol; MK-950; Timolol Maleat; Timolol, maléate de; Timolol, maleato de; Timolol maleinat; Timololi Maleas; Timololimaleaatti; Timololio maleatas; Timololimaleat; Timolol-maleat; Тимонола Малеат.

(*S*)-1-*tert*-Butylamino-3-(4-morpholino-1,2,5-thiadiazol-3-yloxy)propan-2-ol maleate.

$C_{13}H_{24}N_4O_3SC_4H_4O_4$=432.5

CAS — 26839-75-8 (timolol); 91524-16-2 (timolol hemihydrate); 26921-17-5 (timolol maleate).

ATC — C07AA06; S01ED01.

ATC Vet — QC07AA06; QS01ED01.

UNII — P8Y54F701R.

NOTE. TIM is a code approved by the BP 2014 for use on single unit doses of eye drops containing timolol maleate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Timolol Maleate). A white or almost white, crystalline powder or colourless crystals. Soluble in water and in alcohol. A 2% solution in water has a pH of 3.8 to 4.3. Protect from light.

USP 36: (Timolol Maleate). A white to practically white, odourless or practically odourless powder. Soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in chloroform and in propylene glycol; insoluble in cyclohexane and in ether. A 2% solution in water has a pH of 3.8 to 4.3.

Uses and Administration

Timolol is a non-cardioselective beta blocker (p. 1316.3). It is reported to lack intrinsic sympathomimetic and membrane-stabilising activity.

Timolol is used as the maleate in the management of glaucoma (p. 1999.1), hypertension (p. 1251.1), angina pectoris (p. 1254.3), and myocardial infarction (p. 1257.1). It is also used in the prophylactic treatment of migraine (p. 670.3). The hemihydrate is also used.

Eye drops containing timolol maleate or hemihydrate equivalent to 0.25 and 0.5% of timolol are instilled twice daily to reduce **raised intra-ocular pressure** in open-angle **glaucoma** and ocular hypertension. Once-daily use may suffice when the intra-ocular pressure has been controlled. Gel-forming eye drops are also available that are instilled once daily.

For other indications timolol is given orally. In **hypertension** timolol maleate is usually given in initial doses of 10 mg daily, increased according to response at intervals of 7 or more days. Usual maintenance doses are 10 to 40 mg daily, but doses up to 60 mg daily may be required in some patients; doses above 30 mg daily should be given in 2 equally divided doses.

In **angina pectoris** the initial dose is 5 mg twice daily, increased at intervals of 3 or more days by 10 mg daily. Most patients respond to 35 to 45 mg daily in divided doses, but some patients may require up to 60 mg daily.

In patients who have had a **myocardial infarction** timolol maleate is given in initial doses of 5 mg twice daily for 2 days, starting 7 to 28 days after infarction, and increased subsequently in the absence of any contra-indicating adverse effects, to 10 mg twice daily.

Doses of 10 to 20 mg daily of timolol maleate are used in the prophylaxis of **migraine.**

Reduced doses may be required in renal or hepatic impairment.

Adverse Effects, Treatment, and Precautions

As for Beta Blockers, p. 1319.1.

Breast feeding. Timolol is distributed into breast milk. After instillation of timolol 0.5% eye drops twice daily, concentrations of timolol in breast milk of a woman were about 6 times greater than those in serum, the values being 5.6 and 0.93 nanograms/mL respectively.[1] In a study[2] in patients given oral timolol 5 mg three times daily, the mean concentration in breast milk was 15.9 nanograms/mL, and the ratio of milk to plasma concentrations was 0.8; a similar ratio was found at higher doses, and the authors considered that the amount ingested by an infant would not be important. No adverse effects were seen in these studies and the American Academy of Pediatrics considers[3] that timolol is therefore usually compatible with breast feeding.

1. Lustgarten JS, Podos SM. Topical timolol and the nursing mother. *Arch Ophthalmol* 1983; 101: 1381–2.
2. Fidler J, *et al.* Excretion of oxprenolol and timolol in breast milk. *Br J Obstet Gynaecol* 1983; 90: 961–5.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/01/08)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies timolol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

The interactions associated with beta blockers are discussed on p. 1321.2.

Antivirals. US licensed product information for *ritonavir* warns that ritonavir may increase concentrations of timo-

lol and that the dose of timolol may need to be reduced if used together.

Pharmacokinetics

Timolol is almost completely absorbed from the gastrointestinal tract but is subject to moderate first-pass metabolism. Peak plasma concentrations occur about 1 to 2 hours after a dose. Low concentrations are also found in plasma after use as eye drops. Timolol has low to moderate lipid solubility. Protein binding is reported to be low. Timolol crosses the placenta and is distributed into breast milk. A plasma half-life of 4 hours has been reported. Timolol is extensively metabolised in the liver, the metabolites being excreted in the urine with some unchanged timolol. Timolol is not removed by haemodialysis.

Absorption. Reference to the systemic absorption of ophthalmic timolol.[1]

1. Nieminen T, *et al.* Ophthalmic timolol: plasma concentration and systemic cardiopulmonary effects. *Scand J Clin Lab Invest* 2007; 67: 237–45.

Metabolism. Timolol appears to be metabolised[1] by the cytochrome P450 isoenzyme CYP2D6 and studies[2-4] have shown that it is influenced by genetic polymorphism.

1. Volotinen M, *et al.* Timolol metabolism in human liver microsomes is mediated principally by CYP2D6. *Drug Metab Dispos* 2007; 35: 1135–41.
2. McGourty JC, *et al.* Pharmacokinetics and beta-blocking effects of timolol in poor and extensive metabolizers of debrisoquin. *Clin Pharmacol Ther* 1985; 38: 409–13.
3. Lewis RV, *et al.* Timolol and atenolol: relationships between oxidation phenotype, pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol* 1985; 19: 329–33.
4. Lennard MS, *et al.* Timolol metabolism and debrisoquine oxidation polymorphism: a population study. *Br J Clin Pharmacol* 1989; 27: 429–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Atiglauc; Glatim; Ingetim†; Klonalol; Ofal; Plostim; Poentimol; Proflax; Protevis; Timed; Timolert†; Timolpres; Timoptic; Zopirol; *Austral.*: Nyogel; Tenopt; Timoptol; *Austria*: Dispatim; Tim-Ophtal; Timabak†; Timo-COMOD†; Timoftal; Timogel; Timohexal; Timoptic; *Belg.*: Geltim; Nyogel; Nyolol; Timabak; Timo-POS; Timoptol; Timoptolgel; *Braz.*: Glaucotrat; Glautimol; Nyolol; Tenoftal; Timabak; Timoneo; Timoptol; *Canad.*: Apo-Timol; Apo-Timop; Novo-Timol; Tim-Ak; Timoptic; *Chile*: Glausolets; Nyolol; Oculix; Timabak†; Timopt†; Timoptol-XE; Tiof; *China*: Chengrui (诚瑞); Di Li Jian (迪立见); Timoptol (萘慕宁); *Cz.*: Arutimol; Oftan; Ophthalmo-Timogal†; Timo-COMOD; Timohexal; Timoptol; Uni Timolol; *Denm.*: Aquanil†; Nyogel; Optimol; Timacar; Timogel; Timoptol; Timosan; *Fin.*: Betimol†; Blocanol; Timosan; *Fr.*: Digaol†; Geltim; Nyogel; Ophtim; Timabak; Timacor; Timo-COMOD; Timoptol; *Ger.*: Arutimol; Chibro-Timoptol; Dispatim; Nyogel†; Tim-Ophtal; Timo-COMOD; Timo-Stulln; Timo-Vision; TimoEDO; Timohexal†; Timomann; *Gr.*: Betim; Dacrysoline; Flumetol; Geltim; Glafemak; Lithimole; Noval; Nyogel; Nyolol; Temserin; Thilotim; Tim-Alcon; Timabak; Timodose; Waucosin; Yesan; *Hong Kong*: Nyolol; Oftan; Ophtamolol; Optimol†; Timabak; Timoptol; *Hung.*: Arutimol; Cusimolol; Nyolol†; Oftan Timolol; *India*: Glucomol; Glucotim; Iotim; Lopres; Nyolol; O'Clean; Ocobar; Ocu-Lol; Oculan; Ocupres; Ocutim; Optilax; Timolo†; *Indon.*: Isotic Adretor; Kentimol†; Nyolol; Opthil; Tim-Ophtal; Ximex Opticom; *Irl.*: Nyogel; Timofluid; Timoptol; Zanopro Plus; *Israel*: Nyolol; Tiloptic; V-Optic; *Ital.*: Blocadren; Cusimolol; Droptimol; Ialutim; Nyogel; Oftimolo; Timod; Timogel; Timolabak; Timolux; Timoptol; *Jpn*: Timoptol; *Malaysia*: Cusimolol; Optimol; Timo-COMOD; Timolast; Timoptol; *Mex.*: Blocadren; Horex; Imot; Jertz; Nyolol; Shemol; Tenglamol; Timoptol; Timozzard; *Mon.*: Gaoptol; Nyolol; *Neth.*: Nyogel; Timo-COMOD; Timogel; Timoptol; *Norw.*: Blocadren; Oftan; Timosan; *NZ*: Apo-Timol; Apo-Timop; Hypermol†; Timat; Timolux; Timoptol; *Philipp.*: Elevex; Glaucare; Glocure-Opta; I-Supres; Normopres; Nyolol; Ocuper; Oftan; Optamol; Timabak; Timoptol; *Pol.*: Cusimolol; Nyolol; Oftan†; Oftensin; Timo-COMOD†; Timohexal†; Timoptic; *Port.*: Nyogel; Nyolol; Timabak; Timogel; Timoglau; Timolen; Timoptol; *Rus.*: Arutimol (Арутимол); Glautam (Глаутам); Glymol (Глимол); Nyolol (Ниолол); Ocucer (Окуцер); Ocumed (Окумед); Ocumol (Окумол); Ocupres-E (Окупрес-Е); Oftan Timolol (Офтан Тимолол); Optimol (Оптимол); Timadren (Тимадрен); Timo-Komod (Тимо-Комод); Timohexal (Тимогексал); *S.Afr.*: Glaucosan; Nyogel; Timoptol; *Singapore*: Nyolol; Tiamol; Timabak; Timo-COMOD; Timoptol; *Spain*: Cusimolol; Timabak; Timoftol; Timogel; *Swed.*: Blocadren; Optimol; Timosan; *Switz.*: Nyolol; Timisol; Timo-COMOD; Timogel; Timoptic; *Thai.*: Archimol; Glauco-Oph; Nyolol†; Opsartimol; Timo-optal; Timodrop; Timolast†; Timoptol; Timosil; *Turk.*: Cusimolol†; Nyolol; Timabak; Timo-COMOD; Timoftal; Timoptic; Timosol; Timotem; *UK*: Betim; Nyogel†; Timoptol; Tiopex; *Ukr.*: Arutimol (Арутимол); Normatin (Нормятин); Nyolol (Ниолол)†; Ocumed (Окумед); *USA*: Betimol; Blocadren; Isatol; Istalol; Timoptic; *Venez.*: Globitan; Matigel; Matilol; Nyolol; Timoptol.

Multi-ingredient Preparations. *Arg.*: Aliviapres; Azarga; Combigan; Cosopt; Dor-Timolol; Dorlamida T; DuoTrav; Ganfort; Glaucostat T; Glaucotensil TD; Glaucotensil; Latimodorf; Louten T; Ocuprostim; Pilotim; Timed D; Timobrim; Xalacom; Zopirol DM; *Austral.*: Azarga; Combigan; Cosopt; Ganfort; Timpilo†; Xalacom; *Austria*: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Moducrin†; Xalacom; *Belg.*: Azarga; Combigan; Cosopt; DuoTrav; Xalacom; *Braz.*: Combigan; Cosopt; Ganfort; Glaucoftal; Xalacom; *Canad.*: Azarga; Combigan; Cosopt; Duo-Trav; Xalacom; *Chile*: Azarga; Combigan; Cosopt; Dorsof T; Dorzine; DuoTrav; Gaax T; Ganfort; Glaucotensil T; Glausolets Plus; Latof-T; Tiof Plus; Xalacom; *China*: Xalacom (适利加); *Cz.*: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Xalacom; *Denm.*: Alatopran; Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Latanostad Comp; Latiotim; Timosopt†; Xalacom†; Xalcom; *Fin.*: Combigan; Cosopt; Fotil; Glaukostad; Latiotim; Oftastad Comp; Xalcom; *Fr.*: Azarga; Combigan; Cosopt; Duo-Trav; Ganfort; Moducren; Pilobloq†; Xalacom; *Ger.*: Azarga; Combigan; Cosopt; Dorzo Plus T; Dorzolamid comp; DuoTrav; Fotil; Ganfort; Moducrin; TP-Ophtal; Xalacom; *Gr.*: Azarga; Combigan; Cosopt; Dorzoptic Plus; Dorzotim; Dotiz; Dropiltim; DuoTrav; Fotil; Ganfort; Optodrop-Co; T+P; Tesol; Timpilo; Tinoprost; Xalacom; Yvano; *Hong Kong*: Combigan; Cosopt; DuoTrav; Ganfort; Moducren†; Timpilo†; Xalacom; *Hung.*: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Glamzolid; Xalacom; *India*: Brimochek-T; Brimocom; Brimolol; Careprost Plus; Combigan; Ganfort; Iotim-Plus; Laprost Plus; Latim; Latochek-T; Latocom; Misopt; Ocudor-T; *Indon.*: Xalacom; *Irl.*: Azarga; Claropt; Codalux; Combigan; Cosopt; Dortim; DuoTrav; Ganfort; Glaucotima; Lataneau Plus; Moducren†; Prestim; Timlatan; Xalacom; Xaloptic Combi; *Israel*: Combigan; Cosopt; DuoTrav; Ganfort; Timpilo†; Xalacom; *Ital.*: Azarga; Combigan; Cosopt; DuoTrav; Equiton; Ganfort; Glautimol; Pilobloc; Tavu; Timicon; Xalacom†; *Malaysia*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; *Mex.*: Anbigot; Combigan-D; Cosopt; Ganfort; Kryantek; Trovost; Xalacom; *Neth.*: Azarga; Combigan; Cosopt; Dortim; DuoTrav; Fotil†; Ganfort; Latim-POS; Xalacom; *Norw.*: Azarga; Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Latiotim; Xalcom; *NZ*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Timpilo; Xalacom; *Philipp.*: Combigan; Cosopt; DuoTrav; Fotil; Ganfort; Xalacom; *Pol.*: Azarga; Combigan; Cosopt; Dotiteva; DuoTrav; Fotil†; Ganfort; Rozacom; Xalacom; *Port.*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Tavu; Timoglau Plus†; Timosopt†; Xalacom; *Rus.*: Azarga (Азарга); Cosopt (Косопт); Fotil (Фотил); Pilotimol (Пилотимол); Xalacom (Ксалакон); *S.Afr.*: Combigan; Cosopt; DuoTrav; Moducren†; Servatrin; Xalacom; *Singapore*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; *Spain*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Latimvista; Xalacom; *Swed.*: Azarga; Combigan; Cosopt; Costad; DuoTrav; Fotil; Ganfort; Latiotim; Xalcom; *Switz.*: Azarga; Co-Dorzolamid; Co-Latanoprost; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; *Thai.*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; *Turk.*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Xalacom; *UK*: Azarga; Combigan; Cosopt; DuoTrav; Ganfort; Prestim; Xalacom; *Ukr.*: Combigan (Комбиган); Ganfort (Ганфорт); Lanotan T (Лаботан Т); Xalacom (Ксалаком); *USA*: Combigan; Cosopt; Timolide†; *Venez.*: Cosopt; Dobet; Glaucotensil T; Xalacom.

Pharmacopoeial Preparations

BP 2014: Dorzolamide and Timolol Eye Drops; Timolol Eye Drops; Timolol Tablets;
USP 36: Timolol Maleate and Hydrochlorothiazide Tablets; Timolol Maleate Ophthalmic Solution; Timolol Maleate Tablets.

Tinzaparin Sodium *(BAN, USAN, rINN)*

Tintsapariininatrium; Tinzaparin-Natrium; Tinzaparin sodná sůl; Tinzaparin Sodyum; Tinzaparina sódica; Tinzaparine Sodique; Tinzaparinnatrium; Tinzaparin-nátrium; Tinzaparino natrio druska; Tinzaparinum Natricum; Тинзапарин Натрий.

CAS — 9041-08-1.
ATC — B01AB10.
ATC Vet — QB01AB10.
UNII — 35182ET3UA.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tinzaparin Sodium). It is prepared by enzymatic depolymerisation, using heparinase from *Flavobacterium heparinum*, of heparin obtained from the intestinal mucosa of pigs. The majority of the components have a 2-*O*-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-*N*,6-*O*-disulfo-D-glucosamine structure at the reducing end of their chain. The mass-average relative molecular mass ranges between 5500 and 7500, with a characteristic value of about 6500. The mass percentage of chains lower than 2000 is not more than 10%. The degree of sulfation is 1.8 to 2.5 per disaccharide unit.

The potency is not less than 70 units and not more than 120 units of anti-factor Xa activity per mg with reference to the dried substance and the ratio of anti-factor Xa activity to anti-factor IIa (antithrombin) activity is between 1.5 and 2.5.

Units

As for Low-molecular-weight Heparins, p. 1426.2.

Uses and Administration

Tinzaparin sodium is a low-molecular-weight heparin (p. 1426.1) with anticoagulant properties. It is used in the prevention and treatment of venous thromboembolism (p. 1274.1) and to prevent clotting during extracorporea circulation.

For *prophylaxis* of **venous thromboembolism** tinzaparin sodium is given by subcutaneous injection in a variety of dosage regimens. In each case, the duration of treatment is 7 to 10 days.

- For patients at low or intermediate risk, such as those undergoing general surgical procedures, 3500 units of tinzaparin sodium are given 2 hours before the procedure, followed by 3500 units once daily.
- In patients at high risk, such as those undergoing orthopaedic surgery, an initial dose is either 50 units/kg given 2 hours before surgery, or a fixed dose of 4500 units given 12 hours before surgery. The same dose is then given as a once-daily maintenance dose. Alternatively, prophylaxis may be started after surgery at a dose of 75 units/kg once daily.

For the *treatment* of venous thromboembolism tinzaparin sodium is given in a dose of 175 units/kg by subcutaneous injection once daily for at least 6 days and until adequate oral anticoagulation is established. (In pregnant patients, early-pregnancy body-weight should be used to calculate doses.)

For prevention of clotting in the extracorporeal circulation during **haemodialysis**, tinzaparin sodium may be given into the arterial side of the dialyser or intravenously. The dialyser may be primed with 500 to 1000 mL sodium chloride 0.9% containing 5000 units tinzaparin sodium/litre. For dialysis sessions lasting less than 4 hours a single dose of 2000 to 2500 units tinzaparin sodium is given; for longer sessions an initial dose of 2500 units is followed by an infusion of 750 units/hour.

For doses in children, see below.

References.

1. Friedel RA, Balfour JA. Tinzaparin: a review of its pharmacology and clinical potential in the prevention and treatment of thrombo-embolic disorders. *Drugs* 1994; 48: 638–60.
2. Neely JL, *et al.* Tinzaparin sodium: a low-molecular-weight heparin. *Am J Health-Syst Pharm* 2002; 59: 1426–36.
3. Nutescu EA, *et al.* Tinzaparin: considerations for use in clinical practice. *Ann Pharmacother* 2003; 37: 1831–40.
4. Cheer SM, *et al.* Tinzaparin sodium: a review of its pharmacology and clinical use in the prophylaxis and treatment of thromboembolic disease. *Drugs* 2004; 64: 1479–502.
5. Hoy SM, *et al.* Tinzaparin sodium: a review of its use in the prevention and treatment of deep vein thrombosis and pulmonary embolism, and in the prevention of clotting in the extracorporeal circuit during haemodialysis. *Drugs* 2010; 70: 1319–47.

Administration in children. Although tinzaparin is not licensed for use in children in the UK, the *BNFC* suggests that it may be given to children by subcutaneous injection for the prophylaxis and treatment of venous thromboembolism.

For *prophylaxis* of venous thromboembolism, children aged 1 month to 18 years may be given a dose of 50 units/kg once daily.

For *treatment* of venous thromboembolism, the following suggested doses are given according to age:

- 1 to 2 months: 275 units/kg once daily
- 2 months to 1 year: 250 units/kg once daily
- 1 to 5 years: 240 units/kg once daily
- 5 to 10 years: 200 units/kg once daily
- 10 years and over: 175 units/kg once daily

Adverse Effects, Treatment, and Precautions

As for Low-molecular-weight Heparins, p. 1426.3.

Tinzaparin should be avoided in elderly patients with renal failure (see below).

Severe bleeding with tinzaparin sodium may be reduced by the slow intravenous injection of protamine sulfate; 1 mg of protamine sulfate is stated to inhibit the effects of about 100 units of tinzaparin sodium.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tinzaparin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Use in the elderly. An increase in all-cause mortality was seen in patients aged 70 years or older with impaired renal function who were given tinzaparin for the treatment of deep-vein thrombosis or pulmonary embolism. As a result, the FDA recommended that alternatives be considered in these patients while the review of data continued.[1]

1. FDA. Communication about an ongoing safety review of Innohep (tinzaparin sodium injection) (issued 2nd December 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm136254.htm (accessed 03/08/10)

Interactions

As for Low-molecular-weight Heparins, p. 1427.2.

Pharmacokinetics

Tinzaparin sodium is absorbed after subcutaneous injection with a bioavailability of about 90%. Peak plasma activity occurs within 4 to 6 hours. The elimination half-life is about 90 minutes but detectable anti-factor Xa activity may persist for up to 24 hours.

General references.

1. Kuhle S, *et al.* Dose-finding and pharmacokinetics of therapeutic doses of tinzaparin in pediatric patients with thromboembolic events. *Thromb Haemost* 2005; 94: 1164–71.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Innohep; *Canad.*: Innohep; *Denm.*: Innohep; *Fin.*: Innohep; *Fr.*: Innohep; *Ger.*: Innohep; *Gr.*: Innohep; Logiparin; *Hong Kong*: Innohep; *India*: Logiparin; *Irl.*: Innohep; *Malaysia*: Innohep; *Neth.*: Innohep; *Norw.*: Innohep; *NZ*: Innohep; *Philipp.*: Innohep; *Port.*: Innohep; *Singapore*: Innohep; *Spain*: Innohep; *Swed.*: Innohep; *Thai.*: Innohep; *Turk.*: Innohep; *UK*: Innohep; *USA*: Innohep†.

Pharmacopoeial Preparations
BP 2014: Tinzaparin Sodium Injection.

Tirilazad Mesilate *(BANM, rINNM)*

Mesilato de tirilazad; Tirilatsadiinimesilaatti; Tirilazad, Mésilate de; Tirilazad, mesilato de; Tirilazad Mesylate (USAN); Tirilazadi Mesilas; Tirilazadini Mesilas; Tirilazadinmesilat; U-74006F (tirilazad or tirilazad mesilate); Тирилазада Мезилат.

21-[4-(2,6-Di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16α-methylpregna-1,4,9(11)-triene-3,20-dione monomethanesulfonate hydrate.

$C_{38}H_{52}N_6O_2.CH_4O_3S.xH_2O$=721.0 (anhydrous)

CAS — 110101-66-1 (tirilazad); 111793-42-1 (tirilazad mesilate); 149042-61-5 (tirilazad mesilate).

ATC — N07XX01.

ATC Vet — QN07XX01.

UNII — HXS259UWKW (tirilazad mesylate hydrate); 19B418DV39 (anhydrous tirilazad mesylate).

Profile

Tirilazad, a lazaroid, is an inhibitor of lipid peroxidation thought to have a cytoprotective effect against radicals produced in response to tissue trauma. It has been used in the prevention of secondary tissue damage in subarachnoid haemorrhage. It has also been investigated in spinal cord injuries, head injuries, and ischaemic stroke.

References.

1. The Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/06/05).
2. Jang YG, *et al.* Metaanalysis of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care* 2009; 10: 141–7.
3. Zhang S, *et al.* Tirilazad for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2010 (accessed 20/04/10).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Freedox (ФРИДОКС).

Tirofiban Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de tirofibán; L-700462; MK-0383; MK-383; Tirofiban, Chlorhydrate de; Tirofibán, hidrocloruro de; Tirofiban Hidroklorür; Tirofibani Hydrochloridum; Тирофибана Гидрохлорид.

N-(Butylsulfonyl)-4-[4-(4-piperidyl)butoxy]-L-phenylalanine hydrochloride monohydrate.

$C_{22}H_{36}N_2O_5S.HCl.H_2O$=495.1

CAS — 144494-65-5 (tirofiban); 142373-60-2 (anhydrous tirofiban hydrochloride); 150915-40-5 (tirofiban hydrochloride monohydrate).

ATC — B01AC17.

ATC Vet — QB01AC17.

UNII — 6H925F8O5J.

Uses and Administration

Tirofiban hydrochloride is an antiplatelet drug that reversibly inhibits binding of fibrinogen to the glycoprotein IIb/IIIa receptors of platelets. It is given with heparin and aspirin for the management of unstable angina, both in patients managed medically and in those undergoing percutaneous coronary procedures. Tirofiban is used as the hydrochloride, but the dose is expressed in terms of the base; 110 nanograms of tirofiban hydrochloride monohydrate is equivalent to 100 nanograms of tirofiban base.

Tirofiban is given intravenously, at an initial rate of 400 nanograms/kg per minute for 30 minutes, and then continued at 100 nanograms/kg per minute. The recommended duration of treatment is at least 48 hours. Tirofiban infusion may be continued during coronary angiography, and should be maintained for 12 to 24 hours after angioplasty or atherectomy. The entire duration of treatment should not exceed 108 hours.

The dose of tirofiban should be reduced in patients with renal impairment (see below).

General references.

1. McClellan KJ, Goa KL. Tirofiban: a review of its use in acute coronary syndromes. *Drugs* 1998; 56: 1067–80.
2. Menozzi A, *et al.* Tirofiban in acute coronary syndromes. *Expert Rev Cardiovasc Ther* 2005; 3: 193–206.
3. Shanmugam G. Tirofiban and emergency coronary surgery. *Eur J Cardiothorac Surg* 2005; 28: 546–50.
4. Bukow SC, *et al.* Tirofiban for the treatment of ischaemic stroke. *Expert Opin Pharmacother* 2006; 7: 73–9.
5. Mukherjee D, Roffi M. Current strategies with high-dose tirofiban. *Expert Opin Drug Metab Toxicol* 2007; 3: 275–80.
6. Winter JP, Juergens CP. The role of tirofiban in the management of coronary artery disease. *Cardiovasc Hematol Disord Drug Targets* 2008; 8: 138–46.
7. van 't Hof AWJ, Valgimigli M. Defining the role of platelet glycoprotein receptor inhibitors in STEMI: focus on tirofiban. *Drugs* 2009; 69: 85–100.
8. Juwana YB, *et al.* Tirofiban for myocardial infarction. *Expert Opin Pharmacother* 2010; 11: 861–6.

Administration in renal impairment. Patients with renal impairment (creatinine clearance less than 30 mL/minute) should receive half the usual infusion dose of tirofiban.

Ischaemic heart disease. Patients with acute coronary syndromes may be treated either medically or with percutaneous coronary interventions such as angioplasty or stenting. Tirofiban, given with heparin and aspirin, has been tried as adjunctive therapy. A study[1] comparing tirofiban with heparin in the *medical management* of unstable angina (p. 1254.3) or non-Q-wave myocardial infarction reported an initial benefit, at 2 days, of reduced risk of refractory ischaemia, myocardial infarction, or death with tirofiban. This benefit was not maintained at 7 or 30 days after treatment, although a further analysis[2] found that the risk of death or myocardial infarction at 30 days was reduced in patients with raised troponin I concentrations who received tirofiban. In another study,[3] the combination of heparin and tirofiban also reduced the risk of refractory ischaemia, myocardial infarction, or death, compared with heparin alone, and benefit was maintained at 6 months. About half of these patients also underwent revascularisation procedures or surgery if required.

Tirofiban has also been studied in patients undergoing *interventional therapy* (see Reperfusion and Revascularisation Procedures, p. 1259.2), but results have been mixed. The RESTORE study[4] found short-term benefit with tirofiban as an adjunct to heparin in patients undergoing angioplasty or atherectomy for acute coronary syndromes (unstable angina or myocardial infarction), but this was not maintained at 30 days and there was no effect on restenosis after 6 months. However, an observational study[5] in patients with acute myocardial infarction found improved outcomes and studies[6-8] using a higher bolus dose of 25 micrograms/kg have been more promising, including on longer-term follow-up.[6] Pretreatment with tirofiban for 24 to 48 hours before intervention was found to improve angiographic outcomes compared with periprocedural treatment,[9] but there was no difference in clinical events at 30 days. In patients undergoing planned interventions, tirofiban was found to improve outcomes compared with placebo;[10] another study found that it was less effective than abciximab at 30 days,[11] although this difference was no longer apparent after 6 months.[12]

1. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; 338: 1498–1505.
2. Heeschen C, *et al.* Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999; 354: 1757–62.
3. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; 338: 1488–97.
4. Gibson CM, *et al.* Six-month angiographic and clinical follow-up of patients prospectively randomized to receive either tirofiban or placebo during angioplasty in the RESTORE trial. *J Am Coll Cardiol* 1998; 32: 28–34.
5. De Luca G, *et al.* Impact of adjunctive tirofiban administration on myocardial perfusion and mortality in patients undergoing primary angioplasty for ST-segment elevation myocardial infarction. *Thromb Haemost* 2005; 93: 820–3.
6. Valgimigli M, *et al.* The additive value of tirofiban administered with the high-dose bolus in the prevention of ischemic complications during high-risk coronary angioplasty: the ADVANCE Trial. *J Am Coll Cardiol* 2004; 44: 14–19.
7. Valgimigli M, *et al.* Comparison of angioplasty with infusion of tirofiban or abciximab and with implantation of sirolimus-eluting or uncoated stents for acute myocardial infarction: the MULTISTRATEGY randomized trial. *JAMA* 2008; 299: 1788–99.
8. van't Hof AWJ, *et al.* Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet* 2008; 372: 537–46.
9. van 't Hof AWJ, *et al.* A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. *Eur Heart J* 2003; 24: 1401–5.
10. Bonz AW, *et al.* Effect of additional temporary glycoprotein IIb/IIIa receptor inhibition on troponin release in elective percutaneous coronary interventions after pretreatment with aspirin and clopidogrel (TOPSTAR trial). *J Am Coll Cardiol* 2002; 40: 662–8.
11. Topol EJ, *et al.* Comparison of two platelet glycoprotein IIb/IIIa inhibitors, tirofiban and abciximab, for the prevention of ischemic events with percutaneous coronary revascularization. *N Engl J Med* 2001; 344: 1888–94.
12. Molitemo DJ, *et al.* Outcomes at 6 months for the direct comparison of tirofiban and abciximab during percutaneous coronary revascularisation with stent placement: the TARGET follow-up study. *Lancet* 2002; 360: 355–60.

Adverse Effects

Bleeding is the most common adverse effect of tirofiban; others include nausea, headache, fever, rashes and other hypersensitivity reactions, and thrombocytopenia.

Effects on the blood. References to tirofiban-associated thrombocytopenia[1-9] and anaemia.[8]

1. Muiot A, *et al.* Practical approach to the diagnosis and management of thrombocytopenia associated with tirofiban treatment. *Am J Hematol* 2004; 77: 67–71.
2. Patel S, *et al.* Profound thrombocytopenia associated with tirofiban: case report and review of literature. *Angiology* 2005; 56: 351–5.
3. Dunkley S, *et al.* Two distinct subgroups of tirofiban-induced thrombocytopenia exist due to drug dependent antibodies that cause platelet activation and increased ischaemic events. *Platelets* 2005; 16: 462–8.
4. Tuhta AG, *et al.* Tirofiban-associated acute thrombocytopenia. *Acta Cardiol* 2006; 61: 577–9.
5. Clofent-Sanchez G, *et al.* A case of profound and prolonged tirofiban-induced thrombocytopenia and its correction by intravenous immunoglobulin G. *J Thromb Haemost* 2007; 5: 1068–70.
6. Agnelli D, Ottani F. Trombocitopenia grave associata a tirofiban: approccio clinico alla diagnosi e alla gestione terapeutica. *G Ital Cardiol* 2008; 9: 137–43.
7. Beiras-Fernandez A, *et al.* Acute profound thrombocytopenia after treatment with tirofiban and off-pump coronary artery bypass grafting. *Ann Thorac Surg* 2009; 87: 629–31.
8. Sakellariou D, *et al.* First report of tirofiban-induced anemia (found in combination with severe thrombocytopenia). *Tex Heart Inst J* 2009; 36: 55–7.
9. Rahman N, Jafary FH. Vanishing platelets: rapid and extreme tirofiban-induced thrombocytopenia after percutaneous coronary intervention for acute myocardial infarction. *Tex Heart Inst J* 2010; 37: 109–12.

Precautions

As for Abciximab, p. 1282.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tirofiban as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

After stopping an infusion of tirofiban, the antiplatelet effect persists for about 4 to 8 hours. The plasma half-life is about 2 hours. Tirofiban is not highly bound to plasma proteins; the unbound fraction in plasma is about 35%. Tirofiban is eliminated largely unchanged in the urine, with some biliary excretion in the faeces. Tirofiban is removed by haemodialysis.

Reviews.

1. Kondo K, Umemura K. Clinical pharmacokinetics of tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist: comparison with the monoclonal antibody abciximab. *Clin Pharmacokinet* 2002; 41: 187–95.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Agrastat; *Austral.*: Aggrastat; *Austria*: Aggrastat; *Belg.*: Aggrastat; *Braz.*: Agrastat; *Canad.*: Aggrastat; *Chile*: Agrastat; *China*: Aggrastat (艾卡特); Xin Wei Ning (欣维宁); *Cz.*: Aggrastat†; *Fin.*: Aggrastat; *Fr.*: Agrastat; *Ger.*: Aggrastat; *Gr.*: Aggrastat; Avastat; *Hung.*: Aggrastat; *India*: Aggramed; Aggrastat; Aggribloc; Aggritor; GP-2 Ban; *Irl.*: Aggrastat; *Israel*: Aggrastat; *Ital.*: Aggrastat; *Malaysia*: Aggrastat†; *Mex.*: Agrastat; *Neth.*: Aggrastat; *Norw.*: Aggrastat†; *NZ*: Aggrastat; *Philipp.*: Aggrastat; *Pol.*: Aggrastat; *Port.*: Aggrastat; *S.Afr.*: Aggrastet; *Singapore*: Aggrastat; *Spain*: Agrastat; *Swed.*: Aggrastat; *Switz.*: Aggrastat; *Thai.*: Aggrastat; *Turk.*: Aggrastat; *UK*: Aggrastat; *USA*: Aggrastat; *Venez.*: Agrastat.

Tocainide *(BAN, USAN, rINN)*

Tocainida; Tocaïnide; Tocainidum; Tokainid; Tokainidi; W-36095; Токаинид.

2-Aminopropiono-2′,6′-xylidide.

$C_{11}H_{16}N_2O$=192.3

CAS — 41708-72-9.

ATC — C01BB03.

ATC Vet — QC01BB03.
UNII — 27DXO59SAN.

Tocainide Hydrochloride *(BANM, rINNM)*

Hidrocloruro de tocainida; Tocainida, hidrocloruro de; Tocainide, Chlorhydrate de; Tocainidi Hydrochloridum; Токаинида Гидрохлорид.
$C_{11}H_{16}N_2O.HCl=228.7$
CAS — 35891-93-1.
ATC — C01BB03.
ATC Vet — QC01BB03.
UNII — 2K7I38CKN5.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Tocainide Hydrochloride). A fine, white, odourless powder. Freely soluble in water and in alcohol; practically insoluble in chloroform and in ether.

Profile

Tocainide is a class Ib antiarrhythmic (p. 1243.1) with similar properties to mexiletine (p. 1436.2); like mexiletine it is structurally related to lidocaine (p. 1992.1). Tocainide hydrochloride has been given orally and intravenously in the management of ventricular arrhythmias but severe haematological and pulmonary toxicity limit its use.

General references.
1. Holmes B, *et al.* Tocainide: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1983; 26: 93–123.

Preparations

Pharmacopoeial Preparations
USP 36: Tocainide Hydrochloride Tablets.

Tocoferil Nicotinate

Tocoferilo, nicotinato de; Tocopherol Nicotinate; Tocopheryl Nicotinate; Vitamin E Nicotinate; Токоферола Никотинат.
(±)-α-Tocopherol nicotinate.
$C_{35}H_{53}NO_3=535.8$
CAS — 51898-34-1; 16676-75-8.
UNII — WI1J5UCY5C.

NOTE. The names Kenton, NE, Nichi E nate, Nico200, Nicobita-E, Toconijust, Vanarl N, and VE-nicotinate have been used as trade marks for tocoferil nicotinate.

Pharmacopoeias. In *Jpn.*

Profile

Tocoferil nicotinate is a lipid regulating drug and a vasodilator. It is used in the treatment of hyperlipidaemias (p. 1248.1), and in peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2). The usual oral dose is 100 to 200 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ding Rong (顶荣); Qing Zhi Wei (清之维); Wei Er Xin (维尔新); Wei Mai Xin (维麦欣); Weishike (威氏克); *Hong Kong*: Hijuven†; *Indon.*: Enico; *Jpn*: Juvela; *Malaysia*: Hijuven; *Philipp.*: Hijuven†; *Port.*: Reoferol.

Multi-ingredient Preparations. *Arg.*: Anaphase; *Chile*: Anaphase; Anastim; *Fr.*: Anaphase; *Ital.*: Evitex; *Singapore*: Pedimed Foot Care Cream; *Spain*: Evitex A E Puerte; *Venez.*: Anaphase; Anastim.

Todralazine Hydrochloride *(BANM, pINNM)*

BT-621; CEPH; Ecarazine Hydrochloride; Hidrocloruro de todralazina; Todralazina, hidrocloruro de; Todralazine, Chlorhydrate de; Todralazini Hydrochloridum; Todralazyny chlorowodorek; Тодралазина Гидрохлорид.
Ethyl 3-(phthalazin-1-yl)carbazate hydrochloride monohydrate.
$C_{11}H_{12}N_4O_2.HCl.H_2O=286.7$
CAS — 14679-73-3 (todralazine); 3778-76-5 (anhydrous todralazine hydrochloride).
UNII — 5998D60YO0.

Pharmacopoeias. In *Jpn* and *Pol.*

Profile

Todralazine hydrochloride is an antihypertensive structurally related to hydralazine (p. 1401.2) and with similar properties.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Apiracohl†; *Pol.*: Binazin†.

Tolazoline Hydrochloride *(BANM, rINNM)*

Benzazoline Hydrochloride; Hidrocloruro de tolazolina; Tolazol Hydrochlor; Tolazolina, hidrocloruro de; Tolazoline, Chlorhydrate de; Tolazolini Hydrochloridum; Tolazolinium Chloratum; Толазолина Гидрохлорид.
2-Benzyl-2-imidazoline hydrochloride.
$C_{10}H_{12}N_2.HCl=196.7$
CAS — 59-98-3 (tolazoline); 59-97-2 (tolazoline hydrochloride).
ATC — C04AB02; M02AX02.
ATC Vet — QC04AB02; QM02AX02; QV03AB94.
UNII — E669Z651JG.

NOTE. Do not confuse with benazoline, which is a sympathomimetic vasoconstrictor, or with benazolin, which is a herbicide.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Tolazoline Hydrochloride). A white to off-white, crystalline powder. Its solutions are slightly acid to litmus. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 3 of chloroform, and 1 in 10 000 of ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Tolazoline hydrochloride is a vasodilator that has a direct dilator action on the peripheral blood vessels. It has some alpha-adrenoceptor blocking activity and also stimulates smooth muscle in the gastrointestinal tract, increases gastrointestinal secretion, can cause mydriasis, and has a stimulant effect on the heart.

Tolazoline hydrochloride has been used intravenously to reduce pulmonary artery pressure in persistent pulmonary hypertension in neonates with persistent fetal circulation (see below). It has been used orally and by subcutaneous, intramuscular, intravenous, or slow intra-arterial injection in the treatment of peripheral vascular disease. It has also been given in some ophthalmic conditions.

Adverse effects of tolazoline include piloerection, headache, flushing, tachycardia, cardiac arrhythmias, tingling, chilliness, shivering, sweating, nausea, vomiting, diarrhoea, and epigastric pain. Orthostatic hypotension or marked hypertension may occur, especially with large doses. Tolazoline stimulates gastric acid and may exacerbate peptic ulcer disease. Oliguria, haematuria, myocardial infarction, gastrointestinal haemorrhage, thrombocytopenia and other blood dyscrasias have been reported.

Interactions. Tolazoline should not be used with sympathomimetics such as *adrenaline* since the hypotensive effect may be potentiated due to unopposed beta-adrenoceptor stimulation. For a report of fatal hypotension associated with the use of tolazoline with *dopamine*, see Vasodilators under the Interactions of Sympathomimetics, p. 1509.2.

Pulmonary hypertension. Tolazoline and other vasodilators have been tried in persistent pulmonary hypertension in the newborn (p. 1278.2) in an attempt to induce selective pulmonary vasodilatation and improve gas exchange. The response is variable and often unsuccessful due to concomitant systemic hypotension, a failure to achieve or sustain pulmonary vasodilatation, and adverse effects, and other therapies such as high-frequency oscillatory ventilation, extracorporeal membrane oxygenation, and inhaled nitric oxide are now more widely used.

The dose for pulmonary hypertension in neonates that was recommended by licensed product information was an intravenously infused loading dose of 1 to 2 mg/kg, followed by an infusion of 1 to 2 mg/kg per hour. The high incidence of adverse effects, however, led to several studies investigating the use of lower doses. One group suggested that a loading dose of 500 micrograms/kg given intravenously followed by a continuous infusion of 500 micrograms/kg per hour was more appropriate and safer than standard doses.[1] In a retrospective study[2] of extremely preterm infants (mean gestational age 24 weeks) with severe hypoxaemia (possibly attributable to persistent pulmonary hypertension), tolazoline was given as a slow bolus infusion, with most patients receiving a dose of 0.5 to 1 mg/kg; some required further doses.

Tolazoline has also been given via the endotracheal route,[3,4] although as it is acid in solution it may contribute to alveolar injury. In a study[4] of 12 neonates with gestational age ranging from 25 to 42 weeks, endotracheal tolazoline at doses from 1 to 2.5 mg/kg was found to cause no adverse systemic effects.

The *BNFC* gives a dose of 1 mg/kg by slow intravenous injection, followed by 200 micrograms/kg per hour by infusion if necessary. It warns that doses in excess of 300 micrograms/kg per hour are associated with cardiotoxicity and renal failure. A suggested dose for endotracheal use is 200 micrograms/kg diluted in 0.5 to 1 mL of sodium chloride 0.9%.

1. Monin P, *et al.* Treatment of persistent fetal circulation syndrome of the newborn: comparison of different doses of tolazoline. *Eur J Clin Pharmacol* 1987; 31: 569–73.
2. Nuntnarumit P, *et al.* Efficacy and safety of tolazoline for treatment of severe hypoxemia in extremely preterm infants. *Pediatrics* 2002; 109: 852–6.
3. Welch JC, *et al.* Endotracheal tolazoline for severe persistent pulmonary hypertension of the newborn. *Br Heart J* 1995; 73: 99–100.
4. Parida SK, *et al.* Endotracheal tolazoline administration in neonates with persistent pulmonary hypertension. *J Perinatol* 1997; 17: 461–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Divascol.

Multi-ingredient Preparations. *Switz.*: Lunadon†.

Pharmacopoeial Preparations
USP 36: Tolazoline Hydrochloride Injection.

Torasemide *(BAN, rINNM)* ⊗

AC-4464; BM-02015; Torasemid; Torasemid bezvodý; Torasemid, vattenfri; Torasemida; Torasémide; Torasémide anhydre; Torasemidi; Torasemidi, vedetön; Torasemidum; Torasemidum Anhydricum; Torzemidas, bevandenis; Torsemide (USAN); Торасемид.
1-Isopropyl-3-(4-*m*-toluidinopyridine-3-sulphonyl)urea.
$C_{16}H_{20}N_4O_3S=348.4$
CAS — 56211-40-6 (torasemide); 72810-59-4 (torasemide sodium).
ATC — C03CA04.
ATC Vet — QC03CA04.
UNII — W31X2H97FB.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Torasemide, Anhydrous). A white or almost white powder. It exhibits polymorphism. Practically insoluble in water; slightly soluble in alcohol. It is sparingly soluble in dilute solutions of alkali hydroxides and slightly soluble in dilute acids. Protect from light.

USP 36: (Torsemide). A white to off-white, crystalline powder. Practically insoluble in water and in ether; slightly soluble in alcohol, in methyl alcohol, in 0.1N sodium hydroxide, and in 0.1N hydrochloric acid; very slightly soluble in acetone and in chloroform.

Uses and Administration

Torasemide is a loop diuretic with actions similar to those of furosemide (p. 1387.1).

Torasemide is used for oedema associated with heart failure (p. 1262.3), including pulmonary oedema, and with renal and hepatic disorders. It is also used in the treatment of hypertension (p. 1251.1), either alone or with other antihypertensives.

Diuresis after oral use starts within 1 hour, reaches a peak in about 1 to 2 hours, and lasts for up to 8 hours; after intravenous injection its effects are evident within 10 minutes but like oral use can last up to 8 hours.

In the treatment of **oedema** the usual oral dose is 5 mg once daily increased according to response to 20 mg once daily; doses of up to 40 mg daily have been required in some patients. Torasemide may also be given intravenously in usual initial doses of 10 to 20 mg daily. Higher doses may sometimes be necessary, especially in oedema of renal origin; the dose should be increased stepwise as necessary to a maximum of 200 mg daily, although doses should not exceed 40 mg daily in patients with hepatic cirrhosis.

In the treatment of **hypertension** torasemide is given in initial oral doses of 2.5 to 5 mg daily; US licensed product information allows the dose to be increased to 10 mg daily if required, although UK licensed product information suggests that doses above 5 mg are unlikely to produce additional benefit.

Reviews.[1-5] A comparative review of the loop diuretics[5] concluded that torasemide might be more effective and safer than furosemide in the treatment of patients with heart failure, although there was little evidence to support one loop diuretic over another in other oedematous disease states.

1. Blose JS, *et al.* Torsemide: a pyridine-sulfonylurea loop diuretic. *Ann Pharmacother* 1995; 29: 396–402.
2. Dunn CJ, *et al.* Torasemide: an update of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; 49: 121–42.
3. Brater DC. Benefits and risks of torasemide in congestive heart failure and essential hypertension. *Drug Safety* 1996; 14: 104–120.
4. Ishido H, Senzaki H. Torasemide for the treatment of heart failure. *Cardiovasc Hematol Disord Drug Targets* 2008; 8: 127–32.

5. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? *Ann Pharmacother* 2009; 43: 1836–47.

Administration in children. Oral torasemide was shown[1] to be safe and effective in a group of children with heart failure, 62 of whom were newly diagnosed and 40 of whom were switched from furosemide. The children were aged from 3 weeks to 17 years and doses ranged from 180 to 800 micrograms/kg. In those who switched therapy, 1 mg of furosemide was replaced with 200 micrograms of torasemide.

1. Senzaki H, *et al.* Efficacy and safety of torasemide in children with heart failure. *Arch Dis Child* 2008; 93: 768–71.

Adverse Effects and Precautions

As for Furosemide, p. 1388.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies torasemide as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Furosemide, p. 1389.3.

Anticoagulants. For a report of an interaction between torasemide and *warfarin*, see Diuretics under Interactions of Warfarin, p. 1533.3.

Pharmacokinetics

Torasemide is well absorbed from the gastrointestinal tract. Peak serum concentrations occur within 1 hour of oral doses. Torasemide is metabolised by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism. Metabolism takes place in the liver and inactive metabolites are excreted in the urine. The elimination half-life of torasemide is about 3.5 hours. Torasemide is extensively bound to plasma proteins. In patients with heart failure both hepatic and renal clearance are reduced. In patients with renal impairment, the renal clearance is reduced but total plasma clearance is not significantly altered.

References.
1. Knauf H, Mutschler E. Clinical pharmacokinetics and pharmacodynamics of torasemide. *Clin Pharmacokinet* 1998; 34: 1–24.
2. Vormfelde SV, *et al.* CYP2C9 polymorphisms and the interindividual variability in pharmacokinetics and pharmacodynamics of the loop diuretic drug torsemide. *Clin Pharmacol Ther* 2004; 76: 557–66.
3. Werner D, *et al.* Determinants of steady-state torasemide pharmacokinetics: impact of pharmacogenetic factors, gender and angiotensin II receptor blockers. *Clin Pharmacokinet* 2008; 47: 323–32.

Gender. An open-label study[1] in 90 patients found that the area under the concentration-time curve for torasemide was significantly higher, and oral clearance significantly lower, in females compared with males.

1. Werner U, *et al.* Gender is an important determinant of the disposition of the loop diuretic torasemide. *J Clin Pharmacol* 2010; 50: 160–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Torem; *Belg.*: Torrem; *China*: Li Quan (留泉); Li Zhi (留芝); Te Su Min (特苏敏); Te Su Ni (特苏尼); Tuosai (拓赛); Unat (益耐); Yi Mai Ge (伊迈格); Ze Tong (择通); Cz.: Diuver†; *Ger.*: Toracard†; Toragamma†; Torasid†; Torem; Unat; *Gr.*: Unat; *Hong Kong*: Unat; *India*: Demator; Diurator; Dyamide; Dytor; Dytro-Kem; Edeto; *Ital.*: Diuremid; Diuresix; Toradiur; *Jpn*: Luprac; *Pol.*: Diured; Diuver; Trifas; *Rus.*: Diuver (Диувер); Trigrim (Тригрим); *S.Afr.*: ToraHexal; Unat†; *Spain*: Dilutol; Filantor†; Isodiur; Sutril; Tadegan†; *Swed.*: Torem; *Switz.*: Toramide†; Torasem; Torasis†; Torem; *Thai.*: Unat†; *UK*: Torem; *Ukr.*: Britomar (Бритомар); Diuver (Диувер); Torixal (Торихсал); Torsid (Торсид); Trifas (Трифас); Trigrim (Тригрим); *USA*: Demadex.

Multi-ingredient Preparations. *India*: Dyamide Plus; Dytor Plus.

Pharmacopoeial Preparations
USP 36: Torsemide Tablets.

Torcetrapib *(USAN, rINN)*

CP-529414; Torcétrapib; Torcetrapibum; Торцетрапиб.
Ethyl (2*R*,4*S*)-4-[[3,5-bis(trifluoromethyl)benzyl](methoxycarbonyl)amino]-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate.
$C_{26}H_{25}F_9N_2O_4$=600.5
CAS — 262352-17-0.
UNII — 4N4457MV2U.

Profile

Torcetrapib is a cholesteryl ester transfer protein inhibitor. It increases plasma concentrations of high-density lipoprotein (HDL)-cholesterol and has been investigated in the management of lipid disorders. Development was stopped after the finding of increased mortality associated with torcetrapib in randomised, controlled studies.

References.
1. Funder JW. The off-target effects of torcetrapib. *Endocrinology* 2009; 150: 2024–6.

Trandolapril *(BAN, rINN)*

RU-44570; Trandolaprilli; Trandolaprilum; Trandolapryl; Трандолаприл.
Ethyl (2*S*,3a*R*,7a*S*)-1-[(*S*)-*N*-[(*S*)-1-carboxy-3-phenylpropyl]alanyl]hexahydro-2-indolinecarboxylate; (2*S*,3a*R*,7a*S*)-1-[*N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanyl]perhydroindole-2-carboxylic acid.
$C_{24}H_{34}N_2O_5$=430.5
CAS — 87679-37-6.
ATC — C09AA10.
ATC Vet — QC09AA10.
UNII — 1T0N3G9CRC

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; freely soluble in dichloromethane. Protect from light.

USP 36: (Trandolapril). A white or almost white powder. Practically insoluble in water; sparingly soluble in absolute alcohol; freely soluble in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Trandolapril is an ACE inhibitor (p. 1282.2). It is used in the treatment of hypertension (p. 1251.1) and in left ventricular dysfunction following myocardial infarction (p. 1257.1).

Trandolapril owes its activity to trandolaprilat to which it is converted after oral doses. The haemodynamic effects are seen about 1 hour after an oral dose and the maximum effect occurs after 8 to 12 hours. The haemodynamic action lasts for at least 24 hours, allowing once-daily dosing.

In the treatment of **hypertension** the initial oral dose is 500 micrograms once daily. Since there may be a precipitous fall in blood pressure in some patients when starting therapy with an ACE inhibitor, the first dose should preferably be given at bedtime. In patients already taking a diuretic, the diuretic should be stopped, if possible, 2 to 3 days before starting trandolapril and resumed later if necessary. In patients with co-existing heart failure treatment with trandolapril should begin under close medical supervision. The usual maintenance dose for hypertension is 1 to 2 mg once daily, although up to 4 mg daily may be given, as a single dose or in 2 divided doses.

In **myocardial infarction**, treatment with trandolapril may be started 3 days after the infarction in an initial dose of 500 micrograms once daily, gradually increased to a maximum of 4 mg once daily.

A reduction in dosage may be necessary in patients with renal impairment (see below).

References.
1. Zannad F. Trandolapril: How does it differ from other angiotensin converting enzyme inhibitors? *Drugs* 1993; 46 (suppl 2): 172–82.
2. Wiseman LR, McTavish D. Trandolapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in essential hypertension. *Drugs* 1994; 48: 71–90.
3. Kober L, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 1995; 333: 1670–6.
4. Peters DC, *et al.* Trandolapril: an update of its pharmacology and therapeutic use in cardiovascular disorders. *Drugs* 1998; 56: 871–93.
5. Diaz A, Ducharme A. Update on the use of trandolapril in the management of cardiovascular disorders. *Vasc Health Risk Manag* 2008; 4: 1147–58.
6. Ruggenenti P, *et al.* Effect of trandolapril on regression of retinopathy in hypertensive patients with type 2 diabetes: a prespecified analysis of the Benedict trial. *J Ophthalmol* 2010; 2010: 106384.

Administration in renal impairment. The initial dose of trandolapril in patients with renal impairment should not exceed 500 micrograms daily. UK licensed product information states that the maximum maintenance dose should be 2 mg daily in patients with a creatinine clearance of less than 10 mL/minute.

Adverse Effects, Treatment, and Precautions

As for ACE inhibitors, p. 1285.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies trandolapril as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 11/10/11)

Interactions

As for ACE inhibitors, p. 1288.2.

Pharmacokinetics

Trandolapril acts as a prodrug of the diacid trandolaprilat, its active metabolite. After oral doses of trandolapril the bioavailability of trandolaprilat is 40 to 60%. Trandolapril is metabolised in the liver to trandolaprilat and to some inactive metabolites. Peak plasma concentrations of trandolaprilat occur 4 to 6 hours after an oral dose of trandolapril. Trandolaprilat is more than 80% bound to plasma proteins. About 33% of an oral dose of trandolapril is excreted in the urine, mainly as trandolaprilat; the rest is excreted in the faeces. The effective half-life for accumulation of trandolaprilat is 16 to 24 hours after multiple doses of trandolapril.

Impaired renal function decreases the excretion of trandolaprilat. Trandolaprilat is removed by haemodialysis.

References.
1. Bevan EG, *et al.* Effect of renal function on the pharmacokinetics and pharmacodynamics of trandolapril. *Br J Clin Pharmacol* 1993; 35: 128–35.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Dolapril; Gopten; Odrik; Tranalpha; *Braz.*: Gopten; *Canad.*: Mavik; *Cz.*: Fezzor; Gopten; Tanap†; *Denm.*: Fezzor; Odrik; Prilotrand; *Fr.*: Odrik; *Ger.*: Udrik; *Gr.*: Afenil; Daman; Odrik; *Hung.*: Gopten; *Indon.*: Gopten; *Irl.*: Gopten; Odrik; *Ital.*: Gopten; *Jpn*: Odric; Preran; *Neth.*: Gopten; *Norw.*: Gopten; *NZ*: Gopten; Odrik†; *Pol.*: Gopten; Tensotrand; TrandoGen; *Port.*: Gopten; Odrik; *Rus.*: Gopten (Гоптен); *S.Afr.*: Mavik; *Spain*: Gopten; Odrik†; *Switz.*: Gopten; *Turk.*: Gopten; *UK*: Gopten; *USA*: Mavik.

Multi-ingredient Preparations. *Austral.*: Tarka; *Canad.*: Tarka; *Cz.*: Tarka; *Denm.*: Tarka; *Fr.*: Tarka; *Ger.*: Tarka; *Gr.*: Tarka; Ziaxel; *Hong Kong*: Tarka; *Hung.*: Tarka; *Indon.*: Tarka; *Ital.*: Tarka; *Mex.*: Tarka; *Neth.*: Tarka; Ziaxel; *NZ*: Ziaxel†; *Philipp.*: Tarka; *Pol.*: Tarka; *Port.*: Tarka; Ziaxel; *Rus.*: Tarka (Тарка); *S. Afr.*: Tarka; *Spain*: Tarka; Tricen†; *Swed.*: Tarka†; *Switz.*: Tarka; *Turk.*: Tarka; *UK*: Tarka; *Ukr.*: Tarka (Тарка); *USA*: Tarka; *Venez.*: Tarka.

Pharmacopoeial Preparations
BP 2014: Trandolapril Capsules;
USP 36: Trandolapril Tablets.

Trapidil *(BAN, rINN)*

AR-12008; Tarpidil; Trapidilli; Trapidilis; Trapidilum; Трапидил.
7-Diethylamino-5-methyl-1,2,4-triazolo[1,5-*a*]pyrimidine.
$C_{10}H_{15}N_5$=205.3.
CAS — 15421-84-8.
ATC — C01DX11.
ATC Vet — QC01DX11.
UNII — EYG5Y6355E

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Trapidil). A white or almost white crystalline powder. Freely soluble in water; soluble in dehydrated alcohol and in dichloromethane. Protect from light.

Profile

Trapidil is a vasodilator and an inhibitor of platelet aggregation. It is also an antagonist of platelet-derived growth factor. It is used orally in the management of ischaemic heart disease (p. 1254.2) in doses of 400 to 600 mg daily, in divided doses; doses of up to 600 mg daily may be used to prevent restenosis after angioplasty (but see below). Trapidil-eluting stents have also been developed.

References to anti-platelet activity.
1. Yasue H, *et al.* Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction: Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. *Am J Cardiol* 1999; 83: 1308–13.

References to pharmacokinetics.

1. Harder S, *et al.* Pharmacokinetics of trapidil, an antagonist of platelet derived growth factor, in healthy subjects and in patients with liver cirrhosis. *Br J Clin Pharmacol* 1996; 42: 443–9.

Angioplasty and stenting. Although angiographic studies[1-3] have found that trapidil reduces the rate of restenosis after balloon angioplasty (see Reperfusion and Revascularisation Procedures, p. 1259.2), no effect on clinical outcomes[3] has been shown. Studies investigating the use of trapidil after coronary stenting[3,4] have shown no benefit in terms of restenosis or clinical events, and it was concluded that trapidil is not indicated for this purpose. Trapidil-eluting stents have been developed, with some sugges-

tion of benefit in preventing restenosis,[5] although robust evidence is scanty and studies are ongoing.[5,6]

1. Okamoto S, *et al.* Effects of trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, in preventing restenosis after percutaneous transluminal coronary angioplasty. *Am Heart J* 1992; 123: 1439–44.
2. Maresta A, *et al.* Trapidil (triazolopyrimidine), a platelet-derived growth factor antagonist, reduces restenosis after percutaneous transluminal coronary angioplasty: results of the randomized, double-blind STARC study. *Circulation* 1994; 90: 2710–15.
3. Maresta A, *et al.* Starc II, a multicenter randomized placebo-controlled double-blind clinical trial of trapidil for 1-year clinical events and angiographic restenosis reduction after coronary angioplasty and stenting. *Catheter Cardiovasc Interv* 2005; 64: 375–82.
4. Serruys PW, *et al.* The TRAPIST study: a multicentre randomized placebo controlled clinical trial of trapidil for prevention of restenosis after coronary stenting, measured by 3-D intravascular ultrasound. *Eur Heart J* 2001; 22: 1938–47.
5. Khan M, *et al.* Intrepide; Trapidil eluting stent. *EuroIntervention* 2008; 4: 405–11.
6. Iaccarino D, *et al.* Rationale and study design of the OISTER trial: Optical coherence tomography evaluation of stent struts re-endothelialization in patients with non-ST-elevation acute coronary syndromes—a comparison of the intrEpide tRapidil eluting stent vs. taxus drug-eluting stent implantation. *J Cardiovasc Med (Hagerstown)* 2010; 11: 536–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Travisco; *Ger.*: Rocornal; *Ital.*: Travisco; *Jpn*: Rocornal.

Treprostinil *(USAN, rINN)*

15AU81; BW-15AU; BW-15AU81; LRX-15; Tréprostinil; Treprostinilo; Treprostinilum; Treprostinol; U-62840; UT-15; Трепростинил.

((1*R*,2*R*,3a*S*,9a*S*)-2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]-1*H*-benz[*f*]inden-5-yl]oxy)acetic acid.

$C_{23}H_{34}O_5$=390.5

CAS — 81846-19-7.

ATC — B01AC21.

ATC Vet — QB01AC21.

UNII — RUM6K67ESG.

Treprostinil Sodium *(rINNM)*

Natrii Treprostinilum; Tréprostinil Sodique; Treprostinilo sódico; Натрий Трепростинил.

$C_{23}H_{33}NaO_5$=412.5

CAS — 289480-64-4.

ATC — B01AC21.

ATC Vet — QB01AC21.

UNII — 7JZ75N2NT6.

Uses and Administration

Treprostinil, a vasodilator and platelet aggregation inhibitor, is an analogue of the prostaglandin epoprostenol (prostacyclin; p. 1374.3) and is given in the treatment of pulmonary hypertension (p. 1278.2). Treprostinil sodium is given by continuous subcutaneous *infusion*; if this route cannot be tolerated, treprostinil sodium may be given by continuous infusion through a central venous catheter. Doses are calculated in terms of treprostinil: treprostinil sodium 1.32 nanograms is equivalent to about 1.25 nanograms of treprostinil. The infusion is started with a dose equivalent to treprostinil 1.25 nanograms/kg per minute; if this is not tolerated the dose should be halved. The infusion rate can be increased according to patient response, by increments of up to 1.25 nanograms/kg per minute each week for the first 4 weeks, followed by increases of up to 2.5 nanograms/kg per minute each week. There is limited experience with doses above 40 nanograms/kg per minute.

Treprostinil may also be given by *inhalation* in an initial dose of 18 micrograms inhaled 4 times daily, reduced to 6 or 12 micrograms inhaled 4 times daily if the higher dose is not tolerated. Dosage should then be increased in increments of 18 micrograms every 1 to 2 weeks as tolerated, to a maximum maintenance dose of 54 micrograms inhaled 4 times daily.

The dose of treprostinil should be reduced in hepatic impairment, see below.

Intravenous treprostinil has been investigated for intermittent claudication.

References.

1. Moller ER, *et al.* Trial of a novel prostacyclin analog, UT-15, in patients with severe intermittent claudication. *Vasc Med* 2000; 5: 231–7.
2. Simonneau G, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165: 800–804.
3. Vachiéry J-L, *et al.* Transitioning from IV epoprostenol to subcutaneous treprostinil in pulmonary arterial hypertension. *Chest* 2002; 121: 1561–5.
4. Oudiz RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; 126: 420–7.
5. Gomberg-Maitland M, *et al.* Efficacy and safety of sildenafil added to treprostinil in pulmonary hypertension. *Am J Cardiol* 2005; 96: 1334–6.
6. Fernandez B, Strootman D. The prostacyclin analog, treprostinil sodium, provides symptom relief in severe Buerger's disease—a case report and review of literature. *Angiology* 2006; 57: 99–102.
7. Voswinckel R, *et al.* Inhaled treprostinil for treatment of chronic pulmonary arterial hypertension. *Ann Intern Med* 2006; 144: 149–50.
8. Channick RN, *et al.* Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. *J Am Coll Cardiol* 2006; 48: 1433–7.
9. Voswinckel R, *et al.* Favorable effects of inhaled treprostinil in severe pulmonary hypertension: results from randomized controlled pilot studies. *J Am Coll Cardiol* 2006; 48: 1672–81.
10. Skoro-Sajer N, Lang I. Treprostinil for the treatment of pulmonary hypertension. *Expert Opin Pharmacother* 2008; 9: 1415–20.
11. Voswinckel R, *et al.* Metered dose inhaler delivery of treprostinil for the treatment of pulmonary hypertension. *Pulm Pharmacol Ther* 2009; 22: 50–6.
12. Hiremath J, *et al.* TRUST Study Group. Exercise improvement and plasma biomarker changes with intravenous treprostinil therapy for pulmonary arterial hypertension: a placebo-controlled trial. *J Heart Lung Transplant* 2010; 29: 137–49.
13. McLaughlin VV, *et al.* Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. *J Am Coll Cardiol* 2010; 55: 1915–22.

Administration. A study[1] in 23 patients with pulmonary hypertension who were treated with subcutaneous infusion of treprostinil found that a rapid dose-escalation regimen (weekly or twice-weekly increments of 2.5 nanograms/kg per minute) lowered infusion-site pain and improved 12-week exercise outcomes without increasing adverse events when compared with a slower dose-escalation regimen (weekly increments of 1.25 to 2 nanograms/kg per minute).

1. Skoro-Sajer N, *et al.* A clinical comparison of slow- and rapid-escalation treprostinil dosing regimens in patients with pulmonary hypertension. *Clin Pharmacokinet* 2008; 47: 611–18.

Administration in hepatic impairment. Clearance of treprostinil is reduced in patients with hepatic impairment. Licensed product information recommends that the initial dose of the *infusion* should be 0.625 nanograms/kg per minute, and should be increased cautiously, in mild to moderate impairment. No licensed dosage recommendations are given for severe hepatic impairment. However, intravenous treprostinil infusion was reported[1] to be safe and effective in 3 patients with end-stage liver disease, including 1 patient who was given 106 nanograms/kg per minute for 2 years.

Caution is also advocated when titrating upwards from the initial dose of *inhaled* treprostinil in patients with mild to moderate hepatic impairment.

1. Sakai T, *et al.* Initial experience using continuous intravenous treprostinil to manage pulmonary arterial hypertension in patients with end-stage liver disease. *Transpl Int* 2009; 22: 554–61.

Peripheral vascular disease. Prostaglandins have been used for their vasodilating effect in the treatment of peripheral vascular disorders (p. 1272.3), although their role remains unclear. They may be of benefit in severe Raynaud's syndrome (see Vasospastic Arterial Disorders, p. 1275.3) that is complicated by ulceration, and subcutaneous treprostinil was used[1] successfully to treat severe refractory digital necrosis in a patient with Raynaud's disease and scleroderma.

1. Engel G, Rockson SG. Treprostinil for the treatment of severe digital necrosis in systemic sclerosis. *Vasc Med* 2005; 10: 29–32.

Adverse Effects and Precautions

As for Epoprostenol, p. 1375.3; infusion-site reactions are common. Inhaled treprostinil has been associated with signs of local irritation including haemoptysis (fatal in one case), and pneumonia. Treprostinil should be used with caution in hepatic impairment.

Interactions

Since treprostinil is a vasodilator and inhibitor of platelet aggregation, care should be taken in patients receiving other vasodilators or anticoagulants.

Pharmacokinetics

Treprostinil sodium is rapidly and completely absorbed after subcutaneous injection. It is metabolised by the liver and eliminated with a terminal half-life of about 4 hours. About 80% of a dose is excreted in the urine, mainly as metabolites. The systemic absolute bioavailability of inhaled treprostinil is about 64% after an 18 microgram dose and about 72% after a 36 microgram dose.

References.

1. Wade M, *et al.* Absolute bioavailability and pharmacokinetics of treprostinil sodium administered by acute subcutaneous infusion. *J Clin Pharmacol* 2004; 44: 83–8.
2. Wade M, *et al.* Pharmacokinetics of treprostinil sodium administered by 28-day chronic continuous subcutaneous infusion. *J Clin Pharmacol* 2004; 44: 503–9.
3. Laliberte K, *et al.* Pharmacokinetics and steady-state bioequivalence of treprostinil sodium (Remodulin) administered by the intravenous and subcutaneous route to normal volunteers. *J Cardiovasc Pharmacol* 2004; 44: 209–14.
4. McSwain CS, *et al.* Dose proportionality of treprostinil sodium administered by continuous subcutaneous and intravenous infusion. *J Clin Pharmacol* 2008; 48: 19–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Remodulin; *Austral.*: Remodulin; *Austria*: Remodulin; *Belg.*: Remodulin; *Canad.*: Remodulin; *Chile*: Remodulin; *Cz.*: Remodulin; *Denm.*: Remodulin; *Fin.*: Remodulin; *Fr.*: Remodulin; *Ger.*: Remodulin; *Gr.*: Remodulin; *Israel*: Remodulin; Tyvaso; *Ital.*: Remodulin; *Neth.*: Remodulin; *Norw.*: Remodulin; *Port.*: Remodulin; *Swed.*: Remodulin; *Switz.*: Remodulin; *USA*: Remodulin; Tyvaso.

Triamterene *(BAN, USAN, rINN)* ⊗

NSC-77625; SKF-8542; Triamtereeni; Triamteren; Triamterén; Triamterenas; Triamtérène; Triamtereno; Triamterenum; Triantereno; Триамтерен.

6-Phenylpteridine-2,4,7-triamine; 2,4,7-Triamino-6-phenylpteridine.

$C_{12}H_{11}N_7$=253.3

CAS — 396-01-0.

ATC — C03DB02.

ATC Vet — QC03DB02.

UNII — WS821Z52LQ.

NOTE. Compounded preparations of triamterene may be represented by the following names:

- Co-triamterzide (*BAN*)—triamterene 2 parts and hydrochlorothiazide 1 part (w/w)
- Co-triamterzide (*PEN*)—triamterene and hydrochlorothiazide.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Triamterene). A yellow, crystalline powder. Very slightly soluble in water and in alcohol. Protect from light.

USP 36: (Triamterene). A yellow, odourless, crystalline powder. Practically insoluble in water, in chloroform, in ether, in benzene, and in dilute alkali hydroxides; very slightly soluble in alcohol, in acetic acid, and in dilute mineral acids; soluble 1 in 30 of formic acid and 1 in 85 of 2-methoxyethanol. Store in airtight containers. Protect from light.

Uses and Administration

Triamterene is a weak diuretic with potassium-sparing properties which has actions and uses similar to those of amiloride (p. 1299.1). It produces a diuresis in about 2 to 4 hours, with a duration of 7 to 9 hours. The full therapeutic effect may be delayed until after several days of treatment.

Triamterene adds to the natriuretic but diminishes the kaliuretic effects of other diuretics. It is mainly used, as an adjunct to thiazide diuretics such as hydrochlorothiazide and loop diuretics such as furosemide, to conserve potassium in those at risk from hypokalaemia during the treatment of refractory oedema associated with hepatic cirrhosis, heart failure (p. 1262.3), and the nephrotic syndrome. It is also used with other diuretics in the treatment of hypertension (p. 1251.1).

When triamterene is given alone in the treatment of **oedema**, the oral dosage range is 150 to 250 mg daily, given in 2 divided doses, after breakfast and lunch. Doses may be given on alternate days for maintenance therapy. More than 300 mg daily should not be given.

Smaller doses are used initially when other diuretics are also given. When used with hydrochlorothiazide, for example, in the treatment of **hypertension**, an initial dose of 50 mg of triamterene daily may be used.

Potassium supplements should not be given.

Adverse Effects

As for Amiloride Hydrochloride, p. 1299.2. Triamterene has also been reported to cause photosensitivity reactions, increases in uric acid concentrations, and blood dyscrasias. Renal calculi may occur in susceptible patients, and megaloblastic anaemia has been reported in patients with depleted folic acid stores such as those with hepatic cirrhosis. Reversible renal failure, due either to acute interstitial nephritis or to an interaction with NSAIDs (see under Interactions, p. 1519.2) has occurred.

Incidence of adverse effects. In a postmarketing surveillance study of 70 898 patients[1] taking triamterene with hydrochlorothiazide the most common adverse effects were fatigue, dizziness, and nausea. Adverse effects necessitated withdrawal in 8.1% of patients. A subgroup analysis of 21 731 patients[2] indicated that hyperkalaemia was

more common in elderly patients and in those with diabetes mellitus.

1. Hollenberg NK, Mickiewicz CW. Postmarketing surveillance in 70,898 patients treated with a triamterene/hydrochlorothiazide combination (Maxzide). *Am J Cardiol* 1989; 63: 37B–41B.
2. Hollenberg NK, Mickiewicz CW. Hyperkalemia in diabetes mellitus: effect of a triamterene-hydrochlorothiazide combination. *Arch Intern Med* 1989; 149: 1327–30.

Effects on the blood. There have been case reports of pancytopenia associated with triamterene therapy.[1,2] Some patients had hepatic cirrhosis and the antifolate activity of triamterene was considered responsible.[2]

1. Castellano G, *et al.* Pancitopenia aguda y megaloblastosis medular durante el tratemiento con triamterene de la ascitis causada por cirrosis hepática: aportación de dos casos. *Gastroenterol Hepatol* 1983; 6: 540–4.
2. Remacha A, *et al.* Triamterene-induced megaloblastosis: report of two new cases, and review of the literature. *Biol Clin Hematol* 1983; 5: 127–34.

Effects on the kidneys. There have been reports[1–4] of renal calculi containing triamterene or its metabolites, generally in patients also taking hydrochlorothiazide. An abnormal urinary sediment, which was thought to represent precipitated triamterene, was described.[5] These observations were expanded in a crossover study:[6] abnormal urinary sediment was seen in 14 of 26 patients taking triamterene but in none taking amiloride. Triamterene and its metabolites were identified by others in 181 of 50 000 renal calculi.[7] Triamterene either formed the nucleus of the stone or was deposited with calcium oxalate or uric acid. One-third of the 181 stones were entirely or mainly composed of triamterene and its metabolites and it was suggested that supersaturation of the urine with these substances could provide suitable nuclei for the crystallisation of calcium oxalate.[8] However, other workers were unable to confirm this and suggested that triamterene and its metabolites could become incorporated into the protein matrix of existing stones.[9] In addition, an epidemiological study[10] found no evidence that triamterene use was associated with an increased incidence of renal stones. Some authors[11] have therefore considered that there was not enough evidence to contra-indicate the drug in patients with a history of recurrent renal calculi.

Deposition of triamterene in the urine may also play a part in the development of interstitial nephritis, which was diagnosed in 4 patients also taking hydrochlorothiazide, over a period of 4 years.[6]

Triamterene has also been associated with transient decline in renal function and the development of renal failure.[12,13] Several mechanisms may be responsible including interstitial nephritis, intrarenal obstruction by crystalline deposits, and an interaction with NSAIDs (see under Interactions, below).[13] Elderly patients may be particularly at risk.[12]

1. Ettinger B, *et al.* Triamterene-induced nephrolithiasis. *Ann Intern Med* 1979; 91: 745–6.
2. Socolow EL. Triamterene-induced nephrolithiasis. *Ann Intern Med* 1980; 92: 437.
3. Gault MH, *et al.* Triamterene urolithiasis. *Can Med Assoc J* 1981; 124: 1556–7.
4. Grunberg RW, Silberg SJ. Triamterene-induced nephrolithiasis. *JAMA* 1981; 245: 2494–5.
5. Fairley KF, *et al.* Abnormal urinary sediment in patients on triamterene. *Lancet* 1983; i: 421–2.
6. Spence JD, *et al.* Effects of triamterene and amiloride on urinary sediment in hypertensive patients taking hydrochlorothiazide. *Lancet* 1985; ii: 73–5.
7. Ettinger B, *et al.* Triamterene nephrolithiasis. *JAMA* 1980; 244: 2443–5.
8. White DJ, Nancollas GH. Triamterene and renal stone formation. *J Urol (Baltimore)* 1982; 127: 593–7.
9. Werness PG, *et al.* Triamterene urolithiasis: solubility, pK, effect on crystal formation, and matrix binding of triamterene and its metabolites. *J Lab Clin Med* 1982; 99: 254–62.
10. Jick H, *et al.* Triamterene and renal stones. *J Urol (Baltimore)* 1982; 127: 224–5.
11. Woolfson RG, Mansell MA. Does triamterene cause renal calculi? *BMJ* 1991; 303: 1217–18.
12. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; 98: 629–33.
13. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; 51: 454–61.

Effects on the skin. Photodermatitis has been reported in a patient taking triamterene.[1] Pseudoporphyria, possibly associated with exposure to sunlight, occurred in a patient with vitiligo during treatment with triamterene and hydrochlorothiazide.[2]

1. Fernández de Corres L, *et al.* Photodermatitis from triamterene. *Contact Dermatitis* 1987; 17: 114–15.
2. Motley RJ. Pseudoporphyria due to Dyazide in a patient with vitiligo. *BMJ* 1990; 300: 1468.

Precautions

As for Amiloride Hydrochloride, p. 1299.3. Triamterene should also be given with caution to patients with hyperuricaemia or gout, or a history of renal calculi. Patients with depleted folic acid stores such as those with hepatic cirrhosis may be at increased risk of megaloblastic anaemia.

Triamterene may interfere with the fluorescent measurement of quinidine. It may slightly colour the urine blue.

Interactions

As for Amiloride Hydrochloride, p. 1299.3.

Digoxin. For a report of the effect of triamterene on digoxin concentrations, see p. 1357.2.

Dopaminergics. For a report of increased *amantadine* toxicity associated with hydrochlorothiazide and triamterene, see p. 892.2.

NSAIDs. There have been several reports of renal failure in patients taking triamterene and NSAIDs.[1,2] Both types of drug are nephrotoxic and in combination the effect appears to be additive.[3–5] It has been suggested that the suppression of urinary prostaglandins by NSAIDs could potentiate the nephrotoxic effects of triamterene.[1]

NSAIDs may also antagonise the diuretic action of triamterene.[6]

1. Favre L, *et al.* Reversible acute renal failure from combined triamterene and indomethacin: a study in healthy subjects. *Ann Intern Med* 1982; 96: 317–20.
2. Härkönen M, Ekblom-Kullberg S. Reversible deterioration of renal function after diclofenac in patient receiving triamterene. *BMJ* 1986; 293: 698–9.
3. Bailey RR. Adverse renal reactions to non-steroidal anti-inflammatory drugs and potassium-sparing diuretics. *Adverse Drug React Bull* 1988; (Aug.): 492–5.
4. Lynn KL, *et al.* Renal failure with potassium-sparing diuretics. *N Z Med J* 1985; 98: 629–33.
5. Sica DA, Gehr TWB. Triamterene and the kidney. *Nephron* 1989; 51: 454–61.
6. Webster J. Interactions of NSAIDs with diuretics and β-blockers: mechanisms and clinical implications. *Drugs* 1985; 30: 32–41.

Pharmacokinetics

Triamterene is variably but fairly rapidly absorbed from the gastrointestinal tract. The bioavailability has been reported to be about 50%. The plasma half-life has been reported to be about 2 hours. It is estimated to be about 60% bound to plasma proteins. It is extensively metabolised, apparently via the cytochrome P450 isoenzyme CYP1A2, and is mainly excreted in the urine in the form of metabolites with some unchanged triamterene. Triamterene crosses the placenta and may be distributed into breast milk.

References.
1. Pruitt AW, *et al.* Variations in the fate of triamterene. *Clin Pharmacol Ther* 1977; 21: 610–19.
2. Gundert-Remy U, *et al.* Plasma and urinary levels of triamterene and certain metabolites after oral administration to man. *Eur J Clin Pharmacol* 1979; 16: 39–44.
3. Gilfrich HJ, *et al.* Pharmacokinetics of triamterene after iv administration to man: determination of bioavailability. *Eur J Clin Pharmacol* 1983; 25: 237–41.
4. Sörgel F, *et al.* Oral triamterene disposition. *Clin Pharmacol Ther* 1985; 38: 306–12.
5. Fuhr U, *et al.* Rate-limiting biotransformation of triamterene is mediated by CYP1A2. *Int J Clin Pharmacol Ther* 2005; 43: 327–34.

Hepatic impairment. Triamterene clearance was markedly decreased in 7 patients with alcoholic cirrhosis and ascites.[1] The diuretic effect lasted for up to 48 hours in cirrhotic patients compared with 8 hours in healthy controls.

1. Villeneuve JP, *et al.* Triamterene kinetics and dynamics in cirrhosis. *Clin Pharmacol Ther* 1984; 35: 831–7.

Renal impairment. Urinary excretion of triamterene and its metabolite, hydroxytriamterene sulfate, was significantly reduced in patients with renal impairment[1] and in the elderly whose renal function was reduced.[2] Accumulation of the active metabolite was possible in patients with renal impairment.[1]

1. Knauf H, *et al.* Delayed elimination of triamterene and its active metabolite in chronic renal failure. *Eur J Clin Pharmacol* 1983; 24: 453–6.
2. Williams RL, *et al.* Absorption and disposition of two combination formulations of hydrochlorothiazide and triamterene: influence of age and renal function. *Clin Pharmacol Ther* 1986; 40: 226–32.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Dytac; *UK*: Dytac†; *USA*: Dyrenium.

Multi-ingredient Preparations. *Austral.*: Hydrene; *Austria*: Confit; Dytide H; Triamteren comp; Triastad HCT; *Belg.*: Dyta-Urese; Dytenzide; *Braz.*: Diurana; Iguassina; *Canad.*: Apo-Triazide; Novo-Triamzide†; Nu-Triazide†; Pro-Triazide; Riva-Zide; *Chile*: Drinamil; Hidroronol T; Uren; *China*: No 0 (0号); *Fin.*: Furesis comp; Uretren Comp; *Fr.*: Isobar; Prestole; *Ger.*: Beta-Turfa†; dehydro sanol tri; Diu Venostasin; Diucomb; Diuretikum Verla; Dociteren; Dytide H; Neotri; Nephral; Propra comp; Tri-Thiazid; Triampur Compositum; Triamteren comp; Triamteren HCT†; Triamteren tri-comp†; Triarese†; Turfa; Veratide†; *Gr.*: Dyberzide; *Hong Kong*: Apo-Triazide; Dyazide; *India*: Ditide; Frusemene; *Irl.*: Dyazide; *Ital.*: Fluss; *Mex.*: Dyazide†; *Neth.*: Dyta-Urese; Dytenzide; *NZ*: Triamizide†; *Port.*: Dyazide; Triam Tiazida R; *Rus.*: Apo-Triazide (Апо-триазид); Triam-Co (Триам-ко)†; Triampur Compositum (Триампур Композитум); Triamtel (Триамтел); *S.Afr.*: Dyazide; Renezide; *Singapore*: Apo-Triazide; *Spain*: Salidur; *Switz.*: Dyrenium compositum†; *Thai.*: Dinazide; Dyazide; *Turk.*: Triamteril; *UK*: Dyazide; Dytide†; Frusene; Kalspare; Triamco; *Ukr.*: Triampur Compositum (Триампур Композитум); *USA*: Dyazide; Maxzide.

Pharmacopoeial Preparations
BP 2014: Co-triamterzide Tablets; Triamterene Capsules;
USP 36: Triamterene and Hydrochlorothiazide Capsules; Triamterene and Hydrochlorothiazide Tablets; Triamterene Capsules.

Trichlormethiazide *(rINN)* ⊗

Trichlorméthiazide; Trichlormethiazidum; Triclormetiazida; Triklorimetiatsidi; Triklormetiazid; Трихлорметиазид.

6-Chloro-3-dichloromethyl-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulphonamide 1,1-dioxide.

$C_8H_8Cl_3N_3O_4S_2$=380.6

CAS — 133-67-5.

ATC — C03AA06.

ATC Vet — QC03AA06.

UNII — Q58C92TUN0.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Trichlormethiazide). A white or practically white, crystalline powder, odourless or with a slight characteristic odour. Soluble 1 in 1100 of water, 1 in 48 of alcohol, 1 in 5000 of chloroform, 1 in about 4 of dimethylformamide, 1 in about 9 of dioxan, and 1 in 1400 of ether; freely soluble in acetone; soluble in methyl alcohol.

Profile

Trichlormethiazide is a thiazide diuretic with properties similar to those of hydrochlorothiazide (p. 1404.2). It is given orally for oedema, including that associated with heart failure (p. 1262.3), and for hypertension (p. 1251.1).

Diuresis begins about 2 hours after an oral dose, and lasts about 24 hours.

In the treatment of oedema a usual dose has been 1 to 4 mg daily or intermittently. In the treatment of hypertension a usual dose has been 2 to 4 mg daily, either alone, or with other antihypertensives. In some patients 1 mg daily has been adequate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fin.*: Uretren Comp; *Gr.*: Tensiplex; *Jpn*: Irtra.

Pharmacopoeial Preparations
USP 36: Trichlormethiazide Tablets.

Triflusal *(BAN, rINN)*

Triflusaali; Triflusalis; Triflusalum; Trifluzal; UR-1501; Трифлусал.

2-Acetoxy-4-trifluoromethylbenzoic acid; *O*-Acetyl-4-(trifluoromethyl)salicylic acid.

$C_{10}H_7F_3O_4$=248.2

CAS — 322-79-2.

ATC — B01AC18.

ATC Vet — QB01AC18.

UNII — 1Z0YFI05OO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Triflusal). A white or almost white crystalline powder. Practically insoluble in water; very soluble in dehydrated alcohol; freely soluble in dichloromethane. Store in airtight containers at a temperature not exceeding 25 degrees.

Profile

Triflusal reduces platelet aggregation by inhibiting cyclo-oxygenase-1 and phosphodiesterases. It is used in the management of thromboembolic disorders (p. 1273.2) in usual oral doses of 300 to 900 mg daily.

References.
1. Murdoch D, Plosker GL. Triflusal: a review of its use in cerebral infarction and myocardial infarction, and as thromboprophylaxis in atrial fibrillation. *Drugs* 2006; 66: 671–92.
2. González-Correa JA, De La Cruz JP. Triflusal: an antiplatelet drug with a neuroprotective effect? *Cardiovasc Drug Rev* 2006; 24: 11–24.
3. Gómez-Isla T, *et al.* TRIMCI Study Group. A randomized, double-blind, placebo controlled-trial of triflusal in mild cognitive impairment: the TRIMCI study. *Alzheimer Dis Assoc Disord* 2008; 22: 21–9.
4. Anninos H, *et al.* Triflusal: an old drug in modern antiplatelet therapy. Review of its action, use, safety and effectiveness. *Hellenic J Cardiol* 2009; 50: 199–207.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Disgren; *Braz.*: Disgren; *Gr.*: Aflen; Reoflen; *Hung.*: Disgren; *Indon.*: Grendis; *Ital.*: Triflux; *Malaysia*: Grendis; *Mex.*: Disgren; *Philipp.*: Grendis; T-Bren; *Port.*: Tecnosal; *Spain*: Anpeval†; Disgren; *Thai.*: Grendis; *Ukr.*: Disgren (ДИСГРЕН); *Venez.*: Disgren.

Trimetazidine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de trimetazidina; Trimetatsidiinidihydrokloridi; Trimetazidin Hidroklorür; Trimetazidina, hidrocloruro de; Trimetazidindihidrokloridi; Trimetazidindihydrochlorid; Trimetazidin-dihydrochlorid; Trimetazidindihydroklorid; Trimétazidine, Chlorhydrate de; Trimétazidine, dichlorhydrate de; Trimetazidine Dihydrochloride; Trimetazidini dihydrochloridum; Trimetazidini Hydrochloridum; Trimetazidino hidrochloridas; Trimetazine Hydrochloride; Триметазидина Гидрохлорид.

1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride.

$C_{14}H_{22}N_2O_3.2HCl$=339.3

CAS — 5011-34-7 (trimetazidine); 13171-25-0 (trimetazidine hydrochloride).

ATC — C01EB15.

ATC Vet — QC01EB15.

UNII — 48V6723Z1P.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.*

Ph. Eur. 8: (Trimetazidine Dihydrochloride; Trimetazidine Hydrochloride BP 2014). A slightly hygroscopic, white or almost white crystalline powder. Freely soluble in water; sparingly soluble in alcohol. Store in airtight containers.

Profile

Trimetazidine hydrochloride is used in angina pectoris (p. 1254.3); however, following concerns over its questionable efficacy and reports of movement disorders such as parkinsonism, restless legs syndrome, tremor, and gait instability (see Effects on the Nervous System, below), the EMEA in Europe has recommended that trimetazidine should only be used as second-line, add-on therapy in the treatment of stable angina pectoris. The usual dose is 40 to 60 mg given daily in divided oral doses, although higher doses have been used in some countries (as modified-release preparations). It should be given with caution to the elderly and to patients with renal impairment. Therapy should be stopped permanently in patients who develop movement disorders and neurological consultation sought if such adverse effects persist for more than 4 months after stopping the drug.

Trimetazidine has also been used in the symptomatic treatment of vertigo, tinnitus, and Ménière's disease. However, its benefit in these indications has not been shown and the EMEA recommends against such use.

References.

1. McClellan KJ, Plosker GL. Trimetazidine: a review of its use in stable angina pectoris and other coronary conditions. *Drugs* 1999; 58: 143–57.
2. Clappouti A, *et al.* Trimetazidine for stable angina. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 24/01/06).
3. Danchin N. Clinical benefits of a metabolic approach with trimetazidine in revascularized patients with angina. *Am J Cardiol* 2006; 98 (suppl): 8J–13J.
4. Banach M, *et al.* The role of trimetazidine after acute myocardial infarction. *Curr Vasc Pharmacol* 2008; 6: 282–91.
5. Di Napoli P, Taccardi AA. Trimetazidine: the future of cardiac function? *Future Cardiol* 2009; 5: 421–4.
6. Gao D, *et al.* Trimetazidine: a meta-analysis of randomised controlled trials in heart failure. *Heart* 2011; 97: 278–86.
7. Zhang L, *et al.* Additional use of trimetazidine in patients with chronic heart failure: a meta-analysis. *J Am Coll Cardiol* 2012; 59: 913–22.

Effects on the nervous system. Eight elderly patients aged between 72 and 94 years were reported[1] to have developed signs of parkinsonism while taking trimetazidine; the parkinsonism regressed completely when the drug was stopped. A retrospective study[2] found that adverse effects on motor function, including parkinsonism, gait disorders, and tremor, occurred in 56 of 130 patients taking trimetazidine and were more common in older patients.

In June 2012, the EMEA in Europe recommended new contra-indications and warnings to reduce the risk of movement disorders with trimetazidine.[3] The agency was aware of reports of movement disorders such as Parkinsonian symptoms, restless legs syndrome, tremor, and abnormal gait with trimetazidine and advised against its use in patients with a history of such disorders. It was also recommended that treatment with trimetazidine be permanently stopped in those who develop movement disorders.

1. Martí Massó JF. Parkinsonismo por trimetazidina. *Neurologia* 2004; 19: 392–5.
2. Martí Massó J-F, *et al.* Trimetazidine induces parkinsonism, gait disorders and tremor. *Therapie* 2005; 60: 419–22.
3. EMEA. European Medicines Agency recommends restricting use of trimetazidine-containing medicines (issued 22nd June, 2012). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2012/06/WC500129070.pdf (accessed 11/10/12)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Vastarel; *Austria*: Vastarel†; *Braz.*: Vastarel; *Chile*: Vastarel; *China*: Aiyiling (爱怡令); Vasorel (万爽力); Ze Wei Er (泽维尔); *Cz.*: Adexor†; Portora; Preductal; Zilutra; *Denm.*: Vastarel; *Fr.*: Vastarel; *Gr.*: Atanol; Imovexil; Intervein; Latrimet; Liomagen; Novazidine; Trimedin; Trimedor; Trimevert; Vastarel; Zidin; *Hong Kong*: Matenol; Trivedon; Vastarel; *Hung.*: Adexor; Mezitan; Moduxin; Preductal; *India*: Cardimax; Carvidon; Cytogard; Flavedon; Invidon; Isvedon; Kardin; Mayozest; Metacard†; Metagard; Myovedon; Trivedon; *Indon.*: Trizedon; *Irl.*: Vastarel; *Ital.*: Vastarel; *Malaysia*: Metagard†; Metazine; Vastarel; *Philipp.*: Angimax; Angirel; Carvidon; Longity†; Tazinet†; Tazz; Trimerel; Vassapro; Vastarel; Vestar; *Pol.*: Cyto-Protectin; Metazydyna; Preductal; Protevasc; Setal; Trimetaratio; *Port.*: Tacirel; Trimepharma†; Vastarel; *Rus.*: Angiozil (Ангиозил); Angital (Ангитал); Antisten (Антистен); Carditrim (Кардитрим); Deprenorm (Депренорм); Medarum (Медарум); Metagard (Метагард); Prebructal (ПреБРуктал); Predizin (Предизин); Preductal (Предуктал); Rimecor (Римекор); Trimektal (Триметал); Trimet (Тримет); Trimetazide (Триметазид); *Singapore*: Mejadin; Metagard; Vastarel; *Spain*: Idaptan; *Thai.*: Matenol; Metagem; Trizidine; Vastarel; Vastinol; *Turk.*: Sitorel; Vastarel; *Ukr.*: Cardimax (Кардимакс)†; Carductal (Кардуктал); Energoton (Энерготон); Metazidin (Метазидин); Predizin (Предизин); Preductal (Предуктал); Tricard (Трикард); Triductan (Тридуктан); *Venez.*: Vastarel.

Multi-ingredient Preparations. *Ukr.*: Cardasin (Кардазин).

Tripamide *(USAN, rINN)* ⊗

ADR-033; E-614; Tripamida; Tripamidum; Трипамид.

4-Chloro-*N*-(*endo*-hexahydro-4,7-methanoisoindolin-2-yl)-3-sulphamoylbenzamide.

$C_{16}H_{20}ClN_3O_5S$=369.9

CAS — 73803-48-2.

UNII — G36A0E9CVT.

Profile

Tripamide is a diuretic structurally related to indapamide. It is used in the treatment of hypertension.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Normonal; *Thai.*: Normonal.

Urapidil *(BAN, rINN)*

B-66256M; Urapidilii; Urapidilum; Урапидил.

6-[3-(4-o-Methoxyphenylpiperazin-1-yl)propylamino]-1,3-dimethyluracil.

$C_{20}H_{29}N_5O_3$=387.5

CAS — 34661-75-1.

ATC — C02CA06.

ATC Vet — QC02CA06.

UNII — A78GF17HJS.

Pharmacopoeias. In *Jpn.*

Urapidil Hydrochloride *(BANM, rINNM)*

Hidrocloruro de urapidil; Urapidil, Chlorhydrate d'; Urapidil, hidrocloruro de; Urapidilii Hydrochloridum; Урапидила Гидрохлорид.

$C_{20}H_{29}N_5O_3.HCl$=423.9

CAS — 64887-14-5.

ATC — C02CA06.

ATC Vet — QC02CA06.

Uses and Administration

Urapidil is an antihypertensive drug that is reported to block peripheral alpha$_1$ adrenoceptors (see Alpha Blockers, p. 1243.1) and to have central actions. It produces a reduction in peripheral resistance and a fall in systolic and diastolic blood pressure, usually without reflex tachycardia.

Urapidil is used in the management of hypertension (p. 1251.1), including hypertensive crises.

Urapidil is given orally as the base and intravenously as the hydrochloride, but doses are usually expressed in terms of the base. Urapidil hydrochloride 10.94 mg is equivalent to about 10 mg of urapidil. Urapidil fumarate has also been given orally.

In hypertension oral doses of 30 to 90 mg are given twice daily. In hypertensive crises a suggested regimen is to give an initial dose of 25 mg by slow intravenous injection over 20 seconds, repeated if necessary after 5 minutes. This may be followed by a dose of 50 mg after a further 5 minutes if the response is still inadequate. Treatment should continue with a maintenance infusion of 9 to 30 mg/hour once the blood pressure is sufficiently reduced.

Reviews.

1. Dooley M, Goa KL. Urapidil: a reappraisal of its use in the management of hypertension. *Drugs* 1998; 56: 929–55.
2. Buch J. Urapidil, a dual-acting antihypertensive agent: current usage considerations. *Adv Therapy* 2010; 27: 426–43.

Adverse Effects and Precautions

Urapidil is reported to be well-tolerated, with adverse effects generally transient and most frequent at the beginning of therapy. Dizziness, nausea, headache, fatigue, orthostatic hypotension, palpitations, nervousness, pruritus, and allergic skin reactions have been reported.

It should be used with care in elderly patients and those with severe hepatic impairment. Intravenous urapidil should not be used in patients with aortic stenosis.

Urinary incontinence. Enuresis in 2 elderly patients was reported[1] to be associated with the use of urapidil.

1. Jonville A-P, *et al.* Urapidil and enuresis. *Lancet* 1992; 339: 688.

Pharmacokinetics

After oral doses urapidil is rapidly absorbed with a reported bioavailability of 70 to 80%. It is reported to be about 80% bound to plasma proteins. Urapidil is extensively metabolised in the liver, mainly by hydroxylation, and excreted mostly in urine, as metabolites and 10 to 20% of unchanged drug. The elimination half-life is reported to be about 4.7 hours when given orally as capsules and about 2.7 hours after intravenous dosage.

Reviews.

1. Kirsten R, *et al.* Clinical pharmacokinetics of urapidil. *Clin Pharmacokinet* 1988; 14: 129–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Ebrantil; Hypotrit; *Belg.*: Ebrantil; *China*: Ebrantil (亚宁定); Jie Ping (捷平); Jie Tong (捷通); Lao Mai Na (劳麦纳); Lixiding (利喜定); LuoHao (罗浩); Ya Li Di (亚利敌); Yu You Ding (裕优定); *Cz.*: Ebrantil; *Fr.*: Eupressyl; Mediatensyl; *Ger.*: Ebrantil; *Hung.*: Ebrantil; *Ital.*: Ebrantil; *Neth.*: Ebrantil; *Pol.*: Ebrantil; *Port.*: Ebrantil; *Rus.*: Ebrantil (Эбрантил); *Spain*: Elgadil; *Switz.*: Ebrantil; *Ukr.*: Ebrantil (Эбрантил).

Urokinase *(BAN, USAN, rINN)*

Urokinaasi; Urokinas; Urokinasa; Urokinasum; Ūrokinaz; Urokinazė; Urokináz; Uroquinasa; Урокиназа.

CAS — 9039-53-6.

ATC — B01AD04.

ATC Vet — QB01AD04.

UNII — 83G67E21XI.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Urokinase). An enzyme isolated from human urine that activates plasminogen. It consists of a mixture of low (33 000) and high (54 000) molecular mass forms, the high molecular mass form being predominant. The potency is not less than 70 000 international units per mg of protein. A white or almost white, amorphous powder. Soluble in water. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Stability. Solutions of urokinase containing 2500 to 25 000 units/mL were found to be stable in single-use syringes when stored at -30 degrees for 30 days and also when stored frozen for 7 days, thawed, and refrozen for a further 23 days.[1]

1. Dedrick SC, Ramirez-Rico J. Potency and stability of frozen urokinase solutions in syringes. *Am J Health-Syst Pharm* 2004; 61: 1586–9.

Units

The potency of urokinase is expressed in international units. Preparations are assayed using the first International Reference Preparation (1968), a mixture of low-molecular-weight and high-molecular-weight urokinases. The first International Standard for high-molecular-weight urokinase was established in 1989 for use with preparations of this type of urokinase.

Potency used to be expressed in Ploug or Plough units or in CTA units, but these now appear to be obsolete.

Uses and Administration

Urokinase is a thrombolytic produced by the kidney and found in human urine. It directly converts plasminogen to its active form plasmin, resulting in fibrinolysis and dissolution of blood clots. The mechanisms of fibrinolysis are discussed further under Haemostasis and Fibrinolysis on

p. 1124.3. Urokinase affects circulating, unbound plasminogen as well as fibrin-bound plasminogen and thus may be termed a fibrin-nonspecific thrombolytic (see p. 1245.3).

Urokinase is used similarly to streptokinase (p. 1503.1) in the management of thromboembolic disorders including venous thromboembolism (pulmonary embolism and deep-vein thrombosis; p. 1274.1) and peripheral arterial thromboembolism (p. 1273.3). It is also used to clear occluded catheters and cannulas. Urokinase has been used in myocardial infarction and for clearing clots after haemorrhage within the eye.

In the treatment of **venous thromboembolism**, urokinase is given by intravenous infusion in an initial dose of 4400 units/kg given over 10 to 20 minutes. This is followed by maintenance of 4400 units/kg per hour for 12 hours in pulmonary embolism, and for 12 to 24 hours in deep-vein thrombosis; 100 000 units/hour for 2 to 3 days is an alternative maintenance dose for deep-vein thrombosis. Patients with pulmonary embolism may be given urokinase by bolus injection instead, in a dose of 15 000 units/kg into the pulmonary artery. The injection may be given, with the dose adjusted according to plasma-fibrinogen concentration, up to 3 times in 24 hours.

In the treatment of **peripheral arterial thromboembolism**, a solution containing urokinase 2000 units/mL is infused into the clot via a catheter at a rate of 4000 units/minute for 2 hours. Angiography should then be performed and, if flow has not resumed, the catheter should be advanced into the occluded vessel and the infusion continued at the same rate for a further 2 hours. The procedure may be repeated, if necessary, up to 4 times. Once blood flow is re-established, the catheter should be partially withdrawn and infusion continued at a rate of 1000 units/minute until the remaining clot has lysed; a dose of 500 000 units given over 8 hours is usually sufficient.

For **clearing occluded intravenous catheters or cannulas**, 5000 to 25 000 units of urokinase is dissolved in the volume of sodium chloride 0.9% that will completely fill the catheter or cannula, which is then clamped off for 20 to 60 minutes; the lysate is then aspirated and the procedure repeated if necessary. Alternatively, up to 250 000 units may be infused into the device over a period of 90 to 180 minutes using a solution of 1000 to 2500 units/mL in sodium chloride 0.9%.

For doses in children, see below.

Administration in children. Urokinase may be used to clear occluded intravenous catheters and central lines in children in the same dose as for adults, see Uses and Administration, p. 1520.3.

Catheters and cannulas. For reference to the use of urokinase to maintain patency of long-term venous access devices, see under Uses for Alteplase, p. 1297.2.

Adverse Effects, Treatment, and Precautions

As for Streptokinase, p. 1505.1. Serious allergic reactions may be less likely to occur with urokinase than with streptokinase.

Hypersensitivity. Allergic reactions are considered to be less frequent with urokinase than with streptokinase. However, in a series of 6 patients who had previously been treated with streptokinase,[1] thrombolytic therapy with urokinase for recurrent myocardial infarction was associated with rigors in 4 patients, 2 of whom also developed bronchospasm. None of the patients had any history of atopy.

1. Matsis P, Mann S. Rigors and bronchospasm with urokinase after streptokinase. *Lancet* 1992; **340**: 1552.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies urokinase as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Transmission of infection. Some preparations of urokinase are produced in cultures of human cells and there is a risk of transmission of infection associated with their use.

Interactions

As for Streptokinase, p. 1507.1.

Pharmacokinetics

After intravenous infusion urokinase is cleared rapidly from the circulation by the liver. A plasma half-life of up to 20 minutes has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Actosolv; ***China***: LuoXin (洛欣); Sairong (赛溶); Youkai (优凯); ***Cz.***: Rheotromb†; ***Fr.***: Actosolv; Ukidan; ***Ger.***: Corase†; Rheotromb; ***Gr.***: Abbokinase; Syner-Kinase; Ukidan; Urochinasi; ***Hung.***: Rheotromb; ***India***: Dukinase; KD-Unase; Medinase; Solokinase; Uni-Kinase; ***Israel***: Abbokinase†; ***Jpn***: Uronase; ***Neth.***: Medacinase; ***Singapore***: Abbokinase; ***Spain***: Uroquidan†; ***UK***: Syner-Kinase.

Valsartan *(BAN, USAN, rINN)*

CGP-48933; Valsartaani; Valsartán; Valsartanum; Валсартан. *N*-[*p*-(*o*-1*H*-Tetrazol-5-ylphenyl)benzyl]-*N*-valeryl-L-valine; *N*-Pentanoyl-*N*-[2′-(1*H*-tetrazol-5-yl)biphenyl-4-ylmethyl]-L-valine.

$C_{24}H_{29}N_5O_3$=435.5

CAS — 137862-53-4.

ATC — C09CA03.

ATC Vet — QC09CA03.

UNII — 80M03YXJ7I.

Pharmacopoeias. In *US*.

USP 36: (Valsartan). A white or almost white, hygroscopic powder. Practically insoluble in water; freely soluble in anhydrous ethanol; sparingly soluble in dichloromethane. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Suspension. The US licensed product information provides the following method for making 160 mL of a suspension containing valsartan 4 mg/mL:

- add 80 mL of *Ora-Plus* (*Paddock, USA*) to an amber glass bottle containing eight 80-mg tablets (*Diovan, Novartis*) and shake for at least 2 minutes
- allow to stand for at least 1 hour then shake again for at least 1 minute
- add 80 mL of *Ora-Sweet SF* (*Paddock, USA*) to the bottle and shake for at least 10 seconds

The suspension can be stored for 30 days at or below 30 degrees or for up to 75 days at 2 degrees to 8 degrees.

In the UK a licensed oral solution of valsartan 3 mg/mL is available.

Uses and Administration

Valsartan is an angiotensin II receptor antagonist with actions similar to those of losartan (p. 1422.2). It is used in the management of hypertension (p. 1251.1), to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction (p. 1257.1), and in the management of heart failure (see under Losartan Potassium, p. 1423.2).

Valsartan is given orally. After a dose the hypotensive effect occurs within 2 hours, reaches a peak within 4 to 6 hours, and persists for over 24 hours. The maximum hypotensive effect is achieved within 2 to 4 weeks. The doses given below are for tablet and capsule formulations of valsartan; oral liquids are also available (either as a commercial preparation or an extemporaneous preparation) for use in children who have difficulty swallowing tablets (see Administration in Children, below). The bioavailabilities of solid and liquid formulations are not equivalent.

In **hypertension**, valsartan is given in an initial dose of 80 mg once daily. This may be increased, if necessary, to 160 mg once daily; the maximum dose is 320 mg once daily.

In **heart failure**, valsartan is given in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

In patients who have had **myocardial infarction**, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, in an initial dose of 20 mg twice daily; the dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated.

For doses in children, see below.

Valsartan should be used with caution in patients with renal or hepatic impairment and dose reduction may be required in the latter (see below).

Reviews.

1. Markham A, Goa KL. Valsartan: a review of its pharmacology and therapeutic use in essential hypertension. *Drugs* 1997; **54**: 299–311.
2. Ripley TL. Valsartan in chronic heart failure. *Ann Pharmacother* 2005; **39**: 460–9.
3. Mistry NB, *et al*. The angiotensin receptor antagonist valsartan: a review of the literature with a focus on clinical trials. *Expert Opin Pharmacother* 2006; **7**: 575–81.
4. Bissessor N, White H. Valsartan in the treatment of heart failure or left ventricular dysfunction after myocardial infarction. *Vasc Health Risk Manag* 2007; **3**: 425–30.
5. Black HR, *et al*. Valsartan: more than a decade of experience. *Drugs* 2009; **69**: 2393–2414.

Administration in children. Valsartan may be used for hypertension in children aged 6 years and older.

UK licensed product information for tablet formulations includes an initial oral dose of 40 mg once daily for children weighing less than 35 kg, which may be increased to a maximum of 80 mg once daily if necessary. For children weighing 35 kg and over, the suggested initial dose is 80 mg once daily; recommended maximum doses for those weighing 35 to 80 kg are 160 mg once daily, while those weighing 80 kg and over may be given 320 mg once daily. An oral liquid formulation is also available; because of its higher bioavailability this formulation should be started at half the equivalent tablet dose in valsartan-naive patients. If switching from tablets to the oral solution is necessary then the dose should be halved; if switching from the solution to tablets the same dose should be used initially. The dose should be titrated further according to patient response.

US licensed product information for valsartan tablets recommends an initial dose of 1.3 mg/kg once daily (up to a maximum of 40 mg). The dose should be adjusted according to response, but doses above 2.7 mg/kg daily have not been studied. An extemporaneous suspension formulation may be used (see Suspension, above) in children who have difficulty swallowing tablets but exposure to valsartan may be higher with the suspension than with tablets.

There is no experience with valsartan in children with renal impairment (creatinine clearance below 30 mL/minute per 1.73 m^2) and it should therefore not be used in such children.

Administration in hepatic impairment. The elimination of valsartan may be reduced in patients with hepatic impairment or biliary obstruction and it should be used with caution, if at all, in such patients. In the UK, valsartan is contra-indicated in patients with severe hepatic impairment, cirrhosis, or biliary obstruction. In mild to moderate hepatic impairment, the total daily dose should not exceed 80 mg.

Adverse Effects and Precautions

As for Losartan Potassium, p. 1424.1. Valsartan should not be used in those with severe hepatic impairment or when creatinine clearance is less than 10 mL/min, and should be used with caution in patients with mild or moderate renal or hepatic impairment, in cirrhosis, and in biliary obstruction.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies valsartan as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

As for Losartan Potassium, p. 1424.3.

Pharmacokinetics

Valsartan is rapidly absorbed after oral doses, with a bioavailability of about 23% when given as a tablet and about 39% when given as an oral solution. Peak plasma concentrations of valsartan occur 2 to 4 hours after tablets and 1 to 2 hours after oral solution. It is between 94 and 97% bound to plasma proteins. Valsartan is not significantly metabolised and is excreted mainly via the bile as unchanged drug. The terminal elimination half-life is about 6 hours. Following an oral dose about 83% is excreted in the faeces and 13% in urine.

References.

1. Brookman LJ, *et al*. Pharmacokinetics of valsartan in patients with liver disease. *Clin Pharmacol Ther* 1997; **62**: 272–8.
2. Prasad PP, *et al*. Pharmacokinetics of multiple doses of valsartan in patients with heart failure. *J Cardiovasc Pharmacol* 2002; **40**: 801–7.
3. Blumer J, *et al*. Pharmacokinetics of valsartan in pediatric and adolescent subjects with hypertension. *J Clin Pharmacol* 2009; **49**: 235–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alpertan; Corosan; Diovan; Medicoran; Racorval; Sarval; Simultan; ***Austral.***: Diovan; ***Austria***: Diovan; ***Belg.***: Diovane; ***Braz.***: Angio II; Brasart; Diovan; Valsacor; ***Canad.***: Diovan; ***Chile***: Banyass; Dosara; Tareg; Valacor; Valaplex; Valax; Vartalan; Veralpres; ***China***: Da Le (达乐); Diovan (代文); Jia Fei (佳菲); Lizhu Weike (丽珠维可); Ping Xin (平欣); Sui Yue (穗悦); Tuo Ping (托平); Wei Er Tan (维尔坦); Xie Ke (缬克); Yi Fang (怡方); ***Cz.***: Blessin; Cezoryn; Diovan; Kylotan; Valaric; Valmed; Valsacor; Valsanorm; Valsargamma; Valzap; Vanatex; ***Denm.***: Cuenca†; Diovan; Diovane†; Salarvant; Saldanar; Tareg; ValHelen; Valsartamyl†; Valsavil; ***Fin.***: Diovan; Valsarstad; ***Fr.***: Nisis; Tareg; ***Ger.***: Cordinate; Diovan; Provas; Valsacor; ***Gr.***: Avalsan; Dalzad; Diovan; ***Hong Kong***: Diovan; ***Hung.***: Alvastran; Diovan; Nortivan; Tensart; Valsacor; Valsotens; Varexan†; Vezuran; ***India***: Diovan; Starval; ***Indon.***: Diovan; ***Irl.***: Cuenca; Diotev†; Diovan; Saldanar; Valsotens†; Valtan; Vamadrid; Vatan; ***Israel***: Diovan; Vector; ***Ital.***: Alsartan; Cortan; Rixil; Tareg; Valpression; Valsacor; ***Jpn***: Diovan; ***Malay-***

sia: Diovan; *Mex.*: Diovan; *Neth.*: Diovan; Lartavan; Saldanar; Simaldoz; Tifival; Vagrecor; Valcatuna; Valsabio†; Valsanorm; Valsartamib†; Valsavil†; Vamadrid; *Norw.*: Diovan; *Philipp.*: Diovan; *Pol.*: Anartan; Bespres; Diovan; Nortivan; Tensart; Valsacor; Valsotens; Valtap; Valzek; Vanatex; Zelvartan; *Port.*: Diovan; Talsare†; Tanvalir†; Tareg; Varirtan†; Vasanter†; Vatan†; *Rus.*: Diovan (Диован); Nortivan (Нортиван); Valsacor (Вальсакор); Valsaforce (Вальсафорс); Valz (Вальз); *S.Afr.*: Diovan; Migroben; Tareg; Zomevek; *Singapore*: Diovan; *Spain*: Aralter; Diovan; Kalpress; Miten; Vals; *Swed.*: Diovan; *Switz.*: Diovan; *Thai.*: Diovan; Valatan; *Turk.*: Cardopan; Diovan; Premium; Tamgard; *UK*: Diovan; *Ukr.*: Diocor Solo (Диокор Соло); Diovan (Диован); Valsacor (Вальсакор); Valzap (Вальзап); Vasar (Вазар); *USA*: Diovan; *Venez.*: Alsart; Diovan; Vasaten.

Multi-ingredient Preparations. *Arg.*: Alpertan D; Diovan A; Diovan D; Diovan Triple; Exforge D; Exforge; Racorval D; Sarval D; Simultan A; Simultan D; *Austral.*: Co-Diovan; Exforge HCT; Exforge; *Austria*: Co-Angiosan†; Co-Diovan; Exforge HCT; Exforge; *Belg.*: Co-Diovane; Exforge HCT; Exforge; *Braz.*: Diocomb SI; Diovan Amlo; Diovan HCT; Diovan Triplo; *Canad.*: Diovan HCT; *Chile*: Dosara-D; Exforge; Tareg-D; Valacor D; Valaplex-D; Valaxam; Vartalan AM; Vartalan D; Veralpres D; *China*: Co-Diovan (复代文); Exforge (倍博特); Feng Hai Tan (丰海坦); FuTan (福坦); FuXin (复欣); Jia Ze (佳择); Jinxieke (金缬克); Lan Pu (兰普); *Cz.*: Blessin Plus H; Co-Diovan†; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Janartan; Kylotan Plus H; Teval Plus H†; Valsacombi; Valsaratio Plus H; Valzap Combi; Vanatex HCT; Zelvartancombo; *Denm.*: Co-Diovan; Corixil; Cotareg; Diovan Comp; Exforge HCT; Exforge; Tevavaltan comp; Valsavil HCT; Valtension comp; *Fin.*: Diovan Comp; Valsarstad Comp; *Fr.*: Cotareg; Exforge HCT; Exforge; Nisisco; *Ger.*: Co-Diovan; Cordinate plus; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Provas comp; Valsacor comp; Valsartan comp; Valsartan plus HCT; Valsartan/HCT; *Gr.*: Co-Dalzad; Co-Diovan; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; *Hong Kong*: Co-Diovan; Exforge; *Hung.*: Alvastran HCT; Co-Valsacor; Diovan HCT; Exforge; Nortivan HCT; Tensart HCT; Valsartan HCT; Valsotens HCT; Varexan HCT†; *India*: Nebicard-V; *Indon.*: Co-Diovan; Exforge; *Irl.*: Co-Diovan; Co-Vatan; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Valsol Plus; Valtan comp; *Israel*: Co-Diovan; Exforge; Vector Plus; *Ital.*: Combisartan; Corixil; Cotareg; Valbacomp; Validroc; *Malaysia*: Co-Diovan; Exforge; *Mex.*: Co-Diovan; *Neth.*: Co-Diovan; Copalia HCT; Copalia; Cotareg; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT†; Imprida; Valsacell HCT; *Norw.*: Diovan Comp; Exforge HCT; Exforge; *Philipp.*: Co-Diovan; Exforge; *Pol.*: Anartan HCT; Co-Bespres; Co-Diovan; Co-Nortivan; Co-Valsacor; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida HCT; Imprida; Tensart HCT; Valtap HCT; *Port.*: Co-Angiosan; Co-Diovan; Co-Novasan; Co-Tareg; Copalia HCT; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Higo†; Imprida HCT; Imprida; *Rus.*: Co-Diovan (Ко-Диован); Exforge (Эксфорж); Valsacor H (Вальсакор Н); Valsacor HD (Вальсакор НД); Valz H (Вальз Н); *S.Afr.*: Co-Diovan; Co-Migroben; Co-Tareg; Co-Zomevek; Exforge; *Singapore*: Co-Diovan; Exforge HCT; Exforge; *Spain*: Aralter Plus; Co-Diovan; Co-Vals; Copalia; Dafiro HCT; Dafiro; Exforge HCT; Exforge; Imprida; Kalpress Plus; Lefluartil; Miten Plus; *Swed.*: Diovan Comp; Exforge; *Switz.*: Co-Diovan; Exforge HCT; Exforge; *Thai.*: Co-Diovan; Exforge HCT; Exforge; *Turk.*: Cardolex; Cardopan Plus; Co-Diovan; Co-Tamgard; Exforge HCT; Exforge; Premium Plus; *UK*: Co-Diovan; Exforge; *Ukr.*: Co-Diovan (Ко-Диован); Diocor (Диокор); Exforge (Экфорж); Valsacor H (Вальсакор Н); Valsacor HD (Вальсакор НД); Valzap Plus (Вальзап Плюс); Vasar H (Вазар Н); *USA*: Diovan HCT; Exforge HCT; Exforge; *Venez.*: Diovan HCT; Diovan/Amlibon; Vasaten HCT.

Pharmacopoeial Preparations
USP 36: Valsartan and Hydrochlorothiazide Tablets; Valsartan Tablets.

Verapamil Hydrochloride

(BANM, USAN, rINNM)

CP-16533-1 (verapamil); D-365 (verapamil); Hidrocloruro de verapamilo; Iproveratril Hydrochloride; Verapamililhydroklorid; Vérapamil, Chlorhydrate de; Verapamil Hidroklorür; Verapamil-hidroklorid; Verapamilhydrochlorid; Verapamilhydrochlorid; Verapamilhydroklorid; Verapamili hydrochloridum; Verapamilio hidrochloridas; Verapamilo, hidrocloruro de; Верапамила гидрохлорид

5-[*N*-(3,4-Dimethoxyphenethyl)-*N*-methylamino]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride.

$C_{27}H_{38}N_2O_4$,HCl=491.1

CAS — 52-53-9 (verapamil); 152-11-4 (verapamil hydrochloride).

ATC — C08DA01.

ATC Vet — QC08DA01.

UNII — V3888OEYSR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Verapamil Hydrochloride). A white or almost white, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. A 5% solution in water has a pH of 4.5 to 6.0. Protect from light.

USP 36: (Verapamil Hydrochloride). A white or practically white, practically odourless, crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in chloroform; practically insoluble in ether. A 5% solution in water has a pH of 4.5 to 6.5. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Verapamil hydrochloride will precipitate in alkaline solutions. There have been reports of incompatibility with solutions of aminophylline,[1] nafcillin sodium,[2] and sodium bicarbonate.[3]

1. Johnson CE, *et al.* Compatibility of aminophylline and verapamil in intravenous admixtures. *Am J Hosp Pharm* 1989; 46: 97–100.
2. Tucker R, Gentile JP. Precipitation of verapamil in an intravenous line. *Ann Intern Med* 1984; 101: 880.
3. Cutie MR. Verapamil precipitation. *Ann Intern Med* 1983; 98: 672.

Uses and Administration

Verapamil is a phenylalkylamine calcium-channel blocker (p. 1244.2) and a class IV antiarrhythmic (p. 1243.1). It slows conduction through the AV node, and thus slows the increased ventricular response rate that occurs in atrial fibrillation and flutter. Its anti-anginal effect is mainly due to coronary and peripheral vasodilatation, although it also inhibits coronary artery spasm; the decrease in peripheral vascular resistance reduces the work of the heart, which has a sparing effect on myocardial intracellular oxygen consumption. The decrease in peripheral vascular resistance may also explain its antihypertensive effect. Verapamil is used in the control of supraventricular arrhythmias and in the management of angina pectoris and hypertension. It may also be used in the management of myocardial infarction.

Verapamil may be given intravenously or orally, as the hydrochloride; doses are expressed in terms of verapamil hydrochloride.

In the acute management of supraventricular **arrhythmias** it is given intravenously, preferably under continuous ECG and blood pressure monitoring. The initial dose is 5 to 10 mg by slow intravenous injection over 2 to 3 minutes. If necessary, licensed product information in the UK allows a second dose of 5 mg to be given 5 to 10 minutes after the first; in the USA, a second dose of 10 mg may be given after 30 minutes.

Oral doses for the treatment of supraventricular arrhythmias are 120 to 480 mg daily in 3 or 4 divided doses, according to the severity of the condition and the patient's response.

In the management of **angina pectoris**, the usual oral dose is 120 mg three times daily; some patients with angina of effort may respond to 80 mg three times daily, but this lower dose is not likely to be effective in angina at rest or Prinzmetal's variant angina. Modified-release preparations may be given in doses of up to 480 mg daily.

In **hypertension** the usual initial oral dose is 240 mg daily, in 2 or 3 divided doses, adjusted according to response; doses of up to 480 mg daily have been used. Modified-release preparations may be given in similar daily doses.

In the secondary prevention of **myocardial infarction**, verapamil hydrochloride is given as a modified-release oral preparation, started at least 1 week after acute infarction (in patients without heart failure), in a dose of 360 mg daily in divided doses.

Doses of verapamil should be reduced in patients with hepatic impairment (see below).

For doses of verapamil in children with supraventricular arrhythmias or hypertension, see below.

The *R*-enantiomer of verapamil, arverapamil, is under investigation for the treatment of diarrhoea.

General reviews.
1. Brogden RN, Benfield P. Verapamil: a review of its pharmacological properties and therapeutic use in coronary artery disease. *Drugs* 1996; 51: 792–819.
2. Prisant LM. Verapamil revisited: a transition in novel drug delivery systems and outcomes. *Heart Dis* 2001; 3: 55–62.

Administration in children. Verapamil may be used for the treatment of supraventricular arrhythmias and hypertension in children, although great care is needed, especially in infants (see Precautions, p. 1524.3).

Intravenous doses of verapamil hydrochloride for supraventricular arrhythmias are as follows:
- children up to 1 year of age, 100 to 200 micrograms/kg
- 1 to 15 years, 100 to 300 micrograms/kg (to a maximum dose of 5 mg)

The dose should be given over at least 2 minutes and may be repeated after 30 minutes if necessary; doses at the lower end of the range may be adequate and the injection should be stopped when a response has been obtained.

Oral doses for supraventricular arrhythmias or for hypertension are:
- children up to 2 years of age, 20 mg two or three times daily
- 2 years and over, 40 to 120 mg two or three times daily according to age and response

Administration in the elderly. For a discussion of the effects of increasing age on verapamil, see under Pharmacokinetics, p. 1526.1.

Administration in hepatic impairment. Verapamil is extensively metabolised in the liver and should be used with caution in hepatic impairment; US licensed product information recommends that oral doses for patients with severe hepatic impairment should be reduced to about one-third of the usual dose (see Uses and Administration, above).

In a study[1] of patients with liver cirrhosis steady-state plasma concentrations of verapamil were double those seen in patients with normal liver function after intravenous doses and 5 times the normal concentration when given orally. The elimination half-life was prolonged about fourfold after oral or intravenous doses, suggesting that steady-state plasma concentration will not be reached in patients with liver cirrhosis until about 56 hours after therapy has started.

1. Somogyi A, *et al.* Pharmacokinetics, bioavailability and ECG response of verapamil in patients with liver cirrhosis. *Br J Clin Pharmacol* 1981; 12: 51–60.

Administration in renal impairment. The pharmacokinetics and pharmacodynamic effects of verapamil are not significantly altered by renal impairment[1] and dosage adjustment is not considered to be necessary. The elimination of verapamil is not altered by haemodialysis,[1,2] haemofiltration,[2] or peritoneal dialysis[2] and no dosage supplement is required in patients undergoing these procedures.

1. Mooy J, *et al.* Pharmacokinetics of verapamil in patients with renal failure. *Eur J Clin Pharmacol* 1985; 28: 405–10.
2. Beyerlein C, *et al.* Verapamil in antihypertensive treatment of patients on renal replacement therapy—clinical implications and pharmacokinetics. *Eur J Clin Pharmacol* 1990; 39 (suppl 1): S35–S37.

Amaurosis fugax. For a report of the use of verapamil in patients with amaurosis fugax, see under Uses and Administration of Nifedipine, p. 1448.1.

Bipolar disorder. Although lithium and valproate are the mainstays of therapy in bipolar disorder (p. 397.2) many other drugs have been tried, including verapamil.[1] Beneficial responses to verapamil at doses up to 480 mg daily have been reported,[2–4] although a review[5] concluded that there is limited support for its use. Verapamil has also been used with lithium, but there may be an increased risk of neurotoxicity (see under Interactions, p. 1525.3).

1. Höschl C. Do calcium antagonists have a place in the treatment of mood disorders? *Drugs* 1991; 42: 721–29.
2. Dubovsky SL, *et al.* Calcium antagonists in mania: a double-blind study of verapamil. *Psychiatry Res* 1986; 18: 309–20.
3. Giannini AJ, *et al.* Verapamil and lithium in maintenance therapy of manic patients. *J Clin Pharmacol* 1987; 27: 980–2.
4. Wisner KL, *et al.* Verapamil treatment for women with bipolar disorder. *Biol Psychiatry* 2002; 51: 745–52.
5. Levy NA, Janicak PG. Calcium channel antagonists for the treatment of bipolar disorder. *Bipolar Disord* 2000; 2: 108–19.

Box jellyfish sting. Stings by the box jellyfish (*Chironex fleckeri*) (p. 2397.1) can be fatal because of the effects of the venom on the cardiovascular and respiratory systems and on the kidneys. Studies in *rodents* have reported a beneficial effect of intravenous verapamil in the treatment of box jellyfish envenomation, and use in patients with serious box-jellyfish stings has been recommended.[1] However, it has also been suggested[2] that the lack of evidence for benefit and the potential for adverse effects means that use of verapamil should be limited to extreme cases only.

1. Burnett JW. The use of verapamil to treat box-jellyfish stings. *Med J Aust* 1990; 153: 363.
2. Bailey PM, *et al.* Jellyfish envenoming syndromes: unknown toxic mechanisms and unproven therapies. *Med J Aust* 2003; 178: 34–7.

Cardiac arrhythmias. Verapamil has an established role in the management of supraventricular cardiac arrhythmias (p. 1266.1). It is used for rate control in atrial fibrillation and flutter, and may also be used in paroxysmal supraventricular tachycardia. It has been successfully used with digoxin for transplacental therapy in fetal atrial flutter or supraventricular tachycardia,[1,2] although caution is necessary if it is used in infants since they may be particularly susceptible to its adverse effects (see Precautions, p. 1524.3).

1. Maxwell DJ, *et al.* Obstetric importance, diagnosis, and management of fetal tachycardias. *BMJ* 1988; 297: 107–10.
2. Simpson JM, Sharland GK. Fetal tachycardias: management and outcome of 127 consecutive cases. *Heart* 1998; 79: 576–81.

Cardiomyopathies. Verapamil has an established role as a negative inotrope in the management of patients with *hypertrophic cardiomyopathy*,[1,2] although it is usually reserved for patients in whom beta blockers either fail to control symptoms or are not tolerated. It may improve symptoms and exercise tolerance; although a crossover study[3] failed to show an improvement in exercise capacity

with verapamil or the beta blocker nadolol, most patients preferred drug treatment to placebo and there was an apparent improvement in quality of life with verapamil. Verapamil may also be useful for rate control in patients with hypertrophic cardiomyopathy and chronic atrial fibrillation. However, there is no evidence that it reduces the incidence of sudden cardiac death, and serious adverse effects have been reported,[4] especially in patients with severe outflow obstruction. Patients with hypertrophic cardiomyopathy appear to be particularly susceptible to conduction disturbances associated with verapamil, and this may worsen hypotension and outflow obstruction.

Dilated cardiomyopathy is treated similarly to heart failure and calcium-channel blockers are not usually used, although some benefit has been reported with diltiazem (see p. 1359.3).

For a discussion of the management of cardiomyopathies in general, see p. 1261.3.

1. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA* 2002; 287: 1308–20.
2. Maron BJ, *et al.* American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2003; 42: 1687–713. Also published in *Eur Heart J* 2003; 24: 1965–91. Also available at: http://eurheartj.oxfordjournals.org/content/24/21/1965.full.pdf+html (accessed 28/07/10) and at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HCM-FT.pdf (accessed 14/08/08)
3. Gilligan DM, *et al.* A double-blind, placebo-controlled crossover trial of nadolol and verapamil in mild and moderately symptomatic hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993; 21: 1672–9.
4. Epstein SE, Rosing DR. Verapamil: its potential for causing serious complications in patients with hypertrophic cardiomyopathy. *Circulation* 1981; 64: 437–41.

Epilepsy. There are reports[1-3] of the successful use of verapamil in drug-resistant epilepsy (p. 506.1). The mechanism is unknown: modulation of calcium may play a role, although evidence for other calcium-channel blockers as adjuncts in epilepsy has been unconvincing (see under Flunarizine, p. 630.1). An alternative suggestion, that inhibition of P-glycoprotein by verapamil boosts the effect of antiepileptics, remains to be confirmed.

1. Summers MA, *et al.* Use of verapamil as a potential P-glycoprotein inhibitor in a patient with refractory epilepsy. *Ann Pharmacother* 2004; 38: 1631–4.
2. Iannetti P, *et al.* Calcium-channel blocker verapamil administration in prolonged and refractory status epilepticus. *Epilepsia* 2005; 46: 967–9.
3. Iannetti P, *et al.* Addition of verapamil in the treatment of severe myoclonic epilepsy in infancy. *Epilepsy Res* 2009; 85: 89–95.

Kidney disorders. Calcium-channel blockers may be of benefit in various forms of kidney disorder (see Nifedipine, p. 1449.1), although studies with verapamil have suggested that it is less effective than the ACE inhibitor trandolapril in patients with non-diabetic renal disease,[1] and that it does not prevent the development of renal disease in type 2 diabetics.[2] There is some evidence that verapamil may reduce the nephrotoxicity associated with certain drugs, including ciclosporin (see Transplantation, below), and the aminoglycoside gentamicin.[3]

1. Hemmelder MH, *et al.* Antiproteinuric efficacy of verapamil in comparison to trandolapril in non-diabetic renal disease. *Nephrol Dial Transplant* 1999; 14: 98–104.
2. Ruggenenti P, *et al.* for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; 351: 1941–51.
3. Kazierad DJ, *et al.* The effect of verapamil on the nephrotoxic potential of gentamicin as measured by urinary enzyme excretion in healthy volunteers. *J Clin Pharmacol* 1995; 35: 196–201.

Malignant neoplasms. Verapamil has been shown to reverse multidrug resistance to antineoplastics in cultured cells and in *animal* studies,[1] but studies in which verapamil was added to therapy for small cell lung cancer[2] or multiple myeloma[3] failed to show any benefit. See p. 734.2 for a discussion of resistance to antineoplastics.

1. Ford JM, Hait WN. Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev* 1990; 42: 155–99.
2. Milroy R, *et al.* A randomised clinical study of verapamil in addition to combination chemotherapy in small cell lung cancer. *Br J Cancer* 1993; 68: 813–18.
3. Dalton WS, *et al.* A phase III randomized study of oral verapamil as a chemosensitizer to reverse drug resistance in patients with refractory myeloma: a Southwest Oncology Group Study. *Cancer* 1995; 75: 815–20.

Migraine and cluster headache. For reference to the use of calcium-channel blockers, including verapamil, in the management of migraine and cluster headache, see under Nifedipine, p. 1449.1.

Movement disorders. Verapamil has been associated with the development of various movement disorders (see Extrapyramidal Disorders under Adverse Effects of Nifedipine, p. 1452.2) but there have also been case reports[1,2] of its successful use in refractory movement disorders, including severe tardive dyskinesia. However, a systematic review[3] concluded that evidence for the use of verapamil or other calcium-channel blockers in tardive dyskinesia is limited and they are not generally recommended.

The usual management of tardive dyskinesia is discussed under the Adverse Effects of Chlorpromazine, p. 1049.3.

1. Abad V, Ovsiew F. Treatment of persistent myoclonic tardive dystonia with verapamil. *Br J Psychiatry* 1993; 162: 554–6.
2. Ovsiew F, *et al.* Verapamil for severe hyperkinetic movement disorders. *Mov Disord* 1998; 13: 341–4.
3. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/03/07).

Myocardial infarction. Calcium-channel blockers are not routinely used in either the acute or long-term treatment of myocardial infarction (p. 1257.1), although some benefit has been reported with non-dihydropyridines. Diltiazem, started within 24 to 72 hours of the onset of infarction and continued for up to 14 days, has been reported to protect against re-infarction and refractory angina in patients recovering from acute non-Q-wave infarction.[1] A pilot study[2] of intravenous diltiazem as an adjunct to thrombolysis in acute myocardial infarction also suggested a reduction in recurrent ischaemia; diltiazem was given intravenously for 48 hours, beginning at the same time as the thrombolytic, then continued orally for 4 weeks. However, a study[3] with verapamil, started on admission to hospital, found no effect on mortality at 6 months, and there was a suggestion that very early use (within 6 hours of symptom onset) was detrimental. A later study[4] reported that early use of verapamil in patients receiving thrombolysis improved outcome at 90 days. Benefit has also been shown[5] with use of intracoronary verapamil to terminate post-reperfusion arrhythmias. For use of verapamil in patients receiving percutaneous coronary intervention see Reperfusion and Revascularisation Procedures, below.

Although they are not standard therapy, diltiazem and verapamil may be used for long-term management in selected patients without heart failure. In a study by the Multicenter Diltiazem Postinfarction Trial (MDPIT) research group,[6] diltiazem (target dose 240 mg daily) reduced 1-year mortality and re-infarction rates in patients without left ventricular dysfunction, but increased such adverse events in those with left ventricular dysfunction. Re-analysis of the study provided further evidence that diltiazem should be avoided in postinfarction patients with left ventricular dysfunction.[7] Another study[8] in patients with acute myocardial infarction treated with thrombolysis found no reduction in mortality with diltiazem started 36 to 96 hours after infarction and continued for up to 6 months, although the incidence of non-fatal cardiac events was reduced. Patients with heart failure were excluded from the study. In the DAVIT II study[9] late intervention with verapamil (started in the second week after admission) reduced overall mortality, cardiac events, and re-infarction although another study[10] found only a benefit in re-infarction rate and not in overall mortality.

1. Gibson RS, *et al.* Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction: results of a double-blind, randomized, multicenter trial. *N Engl J Med* 1986; 315: 423–9.
2. Théroux P, *et al.* Intravenous diltiazem in acute myocardial infarction: diltiazem as adjunctive therapy to activase (DATA) trial. *J Am Coll Cardiol* 1998; 32: 620–8.
3. The Danish Study Group on Verapamil in Myocardial Infarction. The Danish studies on verapamil in acute myocardial infarction. *Br J Clin Pharmacol* 1986; 21: 197S–204S.
4. Marangelli V, *et al.* Early administration of verapamil after thrombolysis in acute anterior myocardial infarction: effect on left ventricular remodeling and clinical outcome. *Ital Heart J* 2000; 1: 336–43.
5. Kato M, *et al.* Intracoronary verapamil rapidly terminates reperfusion tachyarrhythmias in acute myocardial infarction. *Chest* 2004; 126: 702–8.
6. The Multicenter Diltiazem Postinfarction Trial Research Group. The effect of diltiazem on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1988; 319: 385–92.
7. Goldstein RE, *et al.* Diltiazem increases late-onset congestive heart failure in post-infarction patients with early reduction in ejection fraction. *Circulation* 1991; 83: 52–60.
8. Boden WE, *et al.* Diltiazem in acute myocardial infarction treated with thrombolytic agents: a randomised placebo-controlled trial. *Lancet* 2000; 355: 1751–6.
9. The Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction (the Danish Verapamil Infarction Trial II–DAVIT II). *Am J Cardiol* 1990; 66: 779–85.
10. Rengo F, *et al.* A controlled trial of verapamil in patients after acute myocardial infarction: results of the calcium antagonist reinfarction Italian study (CRIS). *Am J Cardiol* 1996; 77: 365–9.

Peyronie's disease. Verapamil has been used by intraplaque injection for the treatment of Peyronie's disease.[1,2] Pain, curvature, and erectile dysfunction were all improved. A systematic review[2] of 19 studies involving plaque injection therapy for Peyronie's disease, of which 4 used verapamil, noted that although the results of these suggested that injection was safe and effective in mild to moderate Peyronie's disease, the quality of studies was generally poor and its efficacy needed to be verified. Verapamil has also been given by iontophoresis, but again benefits remain unclear. A study[3] comparing verapamil and dexamethasone with lidocaine reported considerable improvement in plaque volume, penile curvature, and pain in the group given verapamil and dexamethasone, while patients given lidocaine had a transient improvement in pain but no change in plaque volume or curvature. However, a study[4] comparing verapamil with sodium chloride as placebo reported some improvement with both treatments, with no difference between the groups.

1. Levine LA, *et al.* Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol (Baltimore)* 2002; 168: 621–5.
2. Russell S, *et al.* Systematic evidence-based analysis of plaque injection therapy for Peyronie's disease. *Eur Urol* 2007; 51: 640–7.
3. Di Stasi SM, *et al.* A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol (Baltimore)* 2004; 171: 1605–8.
4. Greenfield JM, *et al.* Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol (Baltimore)* 2007; 177: 972–5.

Reperfusion and revascularisation procedures. Percutaneous coronary intervention is widely used in the management of patients with acute myocardial infarction and angina pectoris, and adjunctive drug treatment has an important role in reducing complications and improving outcome (see p. 1259.2). Intracoronary verapamil may be used to treat vasospasm[1] and has also been used to treat[2,3] and prevent[4,5] the 'no-reflow' phenomenon. However, transient heart block occurred in some patients given verapamil prophylactically,[5] and this may limit its use.

There is also some evidence that verapamil may reduce the incidence of restenosis after coronary[6] or peripheral[7] percutaneous interventions.

1. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Guidelines for percutaneous coronary interventions. *Eur Heart J* 2005; 26: 804–47. Also available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PCI-FT.pdf (accessed 14/08/08)
2. Piana RN, *et al.* Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994; 89: 2514–18.
3. Demir I, *et al.* Treatment of no-reflow phenomenon with verapamil after primary stent deployment during myocardial infarction. *Jpn Heart J* 2002; 43: 573–80.
4. Rang C-L, *et al.* Early administration of intracoronary verapamil improves myocardial perfusion during percutaneous coronary interventions for acute myocardial infarction. *Chest* 2005; 128: 2593–8.
5. Vijayalakshmi K, *et al.* Prospective, randomised, controlled trial to study the effect of intracoronary injection of verapamil and adenosine on coronary blood flow during percutaneous coronary intervention in patients with acute coronary syndromes. *Heart* 2006; 92: 1278–84.
6. Bestehorn H-P, *et al.* Evaluation of the effect of oral verapamil on clinical outcome and angiographic restenosis after percutaneous coronary intervention: the randomized, double-blind, placebo-controlled, multicenter Verapamil Slow-Release for Prevention of Cardiovascular Events After Angioplasty (VESPA) Trial. *J Am Coll Cardiol* 2004; 43: 2160–5.
7. Schweizer J, *et al.* Effect of high dose verapamil on restenosis after peripheral angioplasty. *J Am Coll Cardiol* 1998; 31: 1299–1305.

Transplantation. Ciclosporin is widely used in transplantation to prevent rejection but its use is limited by its nephrotoxicity. Dihydropyridine calcium-channel blockers (see under Uses of Nifedipine, p. 1450.2) and diltiazem (p. 1360.1) have been reported to reduce ciclosporin-associated nephrotoxicity, and there is some evidence that verapamil may have a similar effect. Studies in renal[1,2] and heart or lung[3] transplant recipients suggested that verapamil can improve outcomes in patients receiving ciclosporin. Most studies have found that verapamil prevents ciclosporin-induced deterioration in renal function, despite increasing plasma-ciclosporin concentrations,[1,2] and there is also evidence[2] that graft survival may be improved. The beneficial effect of verapamil may be related to its ability to protect cells from ischaemia, selective vasodilatation of the afferent renal arterioles, or inherent immunosuppressive properties; its effect on plasma-ciclosporin concentrations may also be involved, either directly[1,2] or by allowing reduction of the ciclosporin dose.[3] However, one study[4] found that use of verapamil with ciclosporin resulted in higher serum-creatinine concentrations in patients given verapamil, with no reduction in the incidence of rejection, and careful monitoring is necessary if the drugs are used together. A higher incidence of severe infections has also been reported[5] in renal transplant patients given verapamil and ciclosporin; the authors suggested that if a rapid increase in plasma-ciclosporin concentrations was required, improved formulations of ciclosporin should be used rather than verapamil.

1. Dawidson I, Rooth P. Improvement of cadaver renal transplantation outcomes with verapamil: a review. *Am J Med* 1991; 90 (suppl 5A): 37S–41S.
2. Dawidson I, *et al.* Verapamil improves the outcome after cadaver renal transplantation. *J Am Soc Nephrol* 1991; 2: 983–90.
3. Chan C, *et al.* A randomized controlled trial of verapamil on cyclosporine nephrotoxicity in heart and lung transplant recipients. *Transplantation* 1997; 63: 1435–40.
4. Pirsch JD, *et al.* A controlled, double-blind, randomized trial of verapamil and cyclosporine in cadaver renal transplant patients. *Am J Kidney Dis* 1993; 21: 189–95.
5. Nanni G, *et al.* Increased incidence of infection in verapamil-treated kidney transplant recipients. *Transplant Proc* 2000; 32: 551–3.

Adverse Effects

Treatment with verapamil is generally well tolerated, but adverse effects connected with its pharmacological effects on cardiac conduction can arise and may be particularly severe in patients with previous myocardial damage or hypertrophic cardiomyopathies. Adverse effects on the heart include bradycardia, AV block, worsening heart

failure, and transient asystole. These effects are more common with parenteral than with oral therapy.

The most troublesome non-cardiac adverse effect is constipation. Nausea may occur but is less frequently reported. Other adverse effects include hypotension, dizziness, flushing, headaches, fatigue, dyspnoea, and peripheral oedema. There have been reports of skin reactions and some cases of abnormal liver function and hepatotoxicity. Gingival hyperplasia has occurred. Gynaecomastia has been reported rarely.

In overdosage there may be severe cardiotoxicity and profound hypotension.

Carcinogenicity. See under Adverse Effects of Nifedipine, p. 1450.3.

Effects on the cardiovascular system. For discussion of the possibility that calcium-channel blockers might be associated with increased cardiovascular mortality, see Effects on Mortality, under Adverse Effects of Nifedipine, p. 1450.2.

Verapamil has vasodilating properties and negative inotropic activity and may cause adverse cardiovascular effects with worsening of arrhythmias. As discussed under Precautions (below) certain cardiac disorders put the patient at risk of severe toxicity.

Some references.

1. Radford D. Side effects of verapamil in infants. *Arch Dis Child* 1983; 58: 465–6.
2. Perrot B, *et al.* Verapamil: a cause of sudden death in a patient with hypertrophic cardiomyopathy. *Br Heart J* 1984; 51: 352–4.
3. Kirk CR, *et al.* Cardiovascular collapse after verapamil in supraventricular tachycardia. *Arch Dis Child* 1987; 62: 1265–6.
4. Mohindra SK, Udeani GO. Long-acting verapamil and heart failure. *JAMA* 1989; 261: 994.
5. Garratt C, *et al.* Degeneration of junctional tachycardia to pre-excited atrial fibrillation after intravenous verapamil. *Lancet* 1989; ii: 219.
6. Stajer D, *et al.* Cardiogenic shock following a single therapeutic oral dose of verapamil. *Int J Clin Pract* 2001; 55: 69–70.
7. Shiraishi H, *et al.* Two cases of polymorphic ventricular tachycardia induced by the administration of verapamil against paroxysmal supraventricular tachycardia. *Intern Med* 2002; 41: 445–8.

Effects on the ears. There have been isolated reports[1] of tinnitus associated with several calcium-channel blockers including nifedipine, nicardipine, nitrendipine, diltiazem, verapamil, and cinnarizine.

1. Narvéez M, *et al.* Tinnitus with calcium-channel blockers. *Lancet* 1994; 343: 1229–30.

Effects on the endocrine system. Hyperprolactinaemia has been reported[1-4] in patients receiving verapamil, and in a few cases[2,3] patients have also had galactorrhoea.

Hyperglycaemia, metabolic acidosis, hyperkalaemia, and bradycardia have occurred[5] after a single dose of modified-release verapamil in a non-diabetic patient who had previously tolerated regular verapamil.

Verapamil has been reported not to affect the release of calcitonin,[6] thyroxine, tri-iodothyronine, thyrotrophin (TSH), follicle-stimulating hormone (FSH), luteinising hormone (LH), or testosterone when given orally;[1] however, intravenous use has been reported to have an inhibitory effect on the release of FSH, LH, and TSH.[7]

1. Semple CG, *et al.* Calcium antagonists and endocrine status: lack of effect of oral verapamil on pituitary-testicular and pituitary-thyroid function. *Br J Clin Pharmacol* 1984; 17: 179–82.
2. Gluskin LE, *et al.* Verapamil-induced hyperprolactinemia and galactorrhea. *Ann Intern Med* 1981; 95: 66–7.
3. Pearrington EL, *et al.* Hyperprolactinemia-galactorrhea induced by verapamil. *Am J Cardiol* 1983; 51: 1466–7.
4. Romeo JH, *et al.* Hyperprolactinaemia and verapamil: prevalence and potential association with hypogonadism in men. *Clin Endocrinol (Oxf)* 1996; 45: 571–5.
5. Roth A, *et al.* Slow-release verapamil and hyperglycemic metabolic acidosis. *Ann Intern Med* 1989; 110: 171–2.
6. Amado JA, *et al.* No effect of verapamil on calcium stimulated calcitonin release. *Postgrad Med J* 1987; 63: 23–4.
7. Barbarino A, De Marinis L. Calcium antagonists and hormone release II: effects of verapamil on basal, gonadotrophin-releasing hormone- and thyrotrophin-releasing hormone-induced pituitary hormone release in normal subjects. *J Clin Endocrinol Metab* 1980; 51: 749–53.

Effects on the gastrointestinal tract. For a report of intestinal pseudo-obstruction related to verapamil use, see under Adverse Effects of Diltiazem, p. 1360.2.

Effects on the liver. Elevated serum concentrations of liver enzymes and bilirubin have been reported during verapamil therapy.[1-5] Clinical symptoms of hepatotoxicity such as abdominal pain, fever, darkened urine, and malaise have also occurred.[2-5] These reactions might have been due to a hypersensitivity reaction and were reversible on stopping verapamil.

1. Brodsky SJ, *et al.* Hepatotoxicity due to treatment with verapamil. *Ann Intern Med* 1981; 94: 490–1.
2. Stern EH, *et al.* Possible hepatitis from verapamil. *N Engl J Med* 1982; 306: 612–13.
3. Nash DT, Feer TD. Hepatic injury possibly induced by verapamil. *JAMA* 1983; 249: 395–6.
4. Guarascio P, *et al.* Liver damage from verapamil. *BMJ* 1984; 288: 362–3.
5. Kumar KL, Colley CA. Verapamil-induced hepatotoxicity. *West J Med* 1994; 160: 485–6.

Effects on the mouth. Gingival hyperplasia[1] and oral mucosal injury[2] have been associated with verapamil therapy. A study involving 115 patients who had received nifedipine, diltiazem, or verapamil for at least 3 months indicated that gingival hyperplasia is an important adverse effect that may occur with calcium-channel blockers in general.[3]

1. Pernu HE, *et al.* Verapamil-induced gingival overgrowth: a clinical, histologic, and biochemic approach. *J Oral Pathol Med* 1989; 18: 422–5.
2. Guttenberg SA. Chemical injury of the oral mucosa from verapamil. *N Engl J Med* 1990; 323: 615.
3. Steele RM, *et al.* Calcium antagonist-induced gingival hyperplasia. *Ann Intern Med* 1994; 120: 663–4.

Effects on the nervous system. There has been a report[1] of 3 patients who complained of unusual perceptual symptoms, described as painful coldness and numbness or bursting feelings, especially in the legs, while taking oral verapamil.

1. Kumana CR, Mahon WA. Bizarre perceptual disorder of extremities in patients taking verapamil. *Lancet* 1981; i: 1324–5.

Effects on the peripheral circulation. Secondary erythermalgia, a vasospastic arterial disorder that may be caused by vasoactive drugs, has been reported[1,2] in patients taking verapamil. Symptoms included burning pain, swelling, and erythema of the hands[2] and feet,[1,2] and resolved when verapamil was stopped. Similar reactions have been reported with nifedipine and other calcium-channel blockers (see p. 1452.1).

1. Drenth JPH, *et al.* Verapamil-induced secondary erythermalgia. *Br J Dermatol* 1992; 127: 292–4.
2. Hart JJ. Painful, swollen, and erythematous hands and feet. *Arthritis Rheum* 1996; 39: 1761–2.

Effects on the respiratory tract. A patient with a history of bronchial asthma developed symptoms of acute asthma after use of a modified-release verapamil preparation;[1] it was possible that excipients, notably alginate, may have been responsible for the reaction.

1. Ben-Noun L. Acute asthma associated with sustained-release verapamil. *Ann Pharmacother* 1997; 31: 593–5.

Effects on sexual function. In a group of 14 men taking verapamil, 3 reported impotence;[1] in 1 patient normal sexual function returned when verapamil was stopped, but impotence recurred on rechallenge.

1. King BD, *et al.* Impotence during therapy with verapamil. *Arch Intern Med* 1983; 143: 1248–9.

Effects on the skin and hair. The commonest skin reactions to verapamil have been rash, pruritus, alopecia, and urticaria;[1] there have been a few reports of erythema multiforme, the Stevens-Johnson syndrome, and exfoliative dermatitis.[1] Hypertrichosis, over many parts of the body, has been reported in a male patient within about 1 month of starting verapamil therapy.[2] In a female patient who had been prematurely grey for about 40 years use of verapamil caused portions of the hair to regrow in its original natural black colour.[3]

1. Stern R, Khalsa JH. Cutaneous adverse reactions associated with calcium channel blockers. *Arch Intern Med* 1989; 149: 829–32.
2. Sever PS. Hypertrichosis and verapamil. *Lancet* 1991; 338: 1215–16.
3. Read GM. Verapamil and hair colour change. *Lancet* 1991; 338: 1520.

Extrapyramidal disorders. Extrapyramidal disorders have been reported with calcium-channel blockers, particularly verapamil (see Nifedipine, p. 1452.2); however, see also p. 1523.1 for reports of the successful use of verapamil in refractory movement disorders.

Haemorrhage. See Effects on the Blood under Adverse Effects of Nifedipine, p. 1450.3.

Overdosage. See under Treatment of Adverse Effects, below.

Treatment of Adverse Effects

As for Nifedipine, p. 1452.3, but see also below.

Verapamil is not removed by dialysis.

Overdosage. The consequences and treatment of overdosage with verapamil are similar to those with other calcium-channel blockers (see Treatment of Adverse Effects under Nifedipine, p. 1452.3), although death and life-threatening complications may be more common with non-dihydropyridines such as verapamil; several fatalities have occurred.[1]

Individual reports of overdosage with verapamil have included:

- A patient[2] who took 3.2 g of verapamil developed bradycardia and hypotension, which responded to intravenous calcium gluconate injection. A continuous infusion of calcium gluconate was given for 12 hours to maintain sinus rhythm. The blood-verapamil concentration measured 5 hours after ingestion was 4 micrograms/mL.
- A patient[3] presented with loss of consciousness, severe hypotension, and bradycardia up to 18 hours after taking at least 1.2 g of verapamil. Treatment with glucagon, prenalterol, and atropine was unsuccessful, and there was a minimal response to intravenous calcium gluconate. Dobutamine and isoprenaline were given to maintain the blood pressure and mechanical ventilation was required for 24 hours, during which time metabolic acidosis and hyperglycaemia developed. The patient survived with cerebral anoxic damage.
- A patient[4] who had taken an unknown amount of verapamil developed cyanosis, undetectable blood pressure, and complete heart block. There was some response to sympathomimetics and calcium gluconate, although pacing was necessary to reverse the bradycardia. However, hypotension unresponsive to sympathomimetics developed after an episode of asystole and the patient died 19 hours after admission. The serum-verapamil concentration 12 hours after admission was 3 micrograms/mL.
- Haematemesis occurred in a patient[5] who took 3.2 g of verapamil; gastric ulceration was found on gastroscopy 12 hours after admission.

Overdosage with modified-release preparations of verapamil may result in prolonged toxicity of delayed onset.[6] Intravenous infusion of a fat emulsion, which can attenuate the cardiotoxicity of lipophilic drugs (see Soya Oil, p. 2093.1), was of benefit in a patient with refractory shock after a multidrug overdose including 13.44 g of verapamil in a modified-release formulation.[7] Conventional-release preparations may also produce prolonged toxicity; elimination half-life was reported to be prolonged to 15 hours and peak plasma concentrations delayed to 6 to 7 hours in a 59-year-old man after ingestion of 2.4 g of verapamil.[8] Rate-limiting absorption at high doses was considered to be the cause.

Although severe toxicity usually relates to acute verapamil overdosage, similar symptoms have also been reported with chronic toxicity. Long-term treatment with verapamil 240 mg daily[9] in a patient with cirrhosis of the liver led to loss of consciousness, cardiogenic shock, cyanosis, hypotension, severe acidosis, hyperkalaemia, hypothermia, and renal failure. The patient recovered after treatment with high doses of dopamine, noradrenaline, sodium bicarbonate, and sodium chloride.

1. Hofer CA, *et al.* Verapamil intoxication: a literature review of overdoses and discussions of therapeutic options. *Am J Med* 1993; 95: 431–8.
2. Perkins GM. Serious verapamil poisoning: treatment with intravenous calcium gluconate. *BMJ* 1978; 2: 1127.
3. Crump BJ, *et al.* Lack of response to intravenous calcium in severe verapamil poisoning. *Lancet* 1982; ii: 939–40.
4. Orr GM, *et al.* Fatal verapamil overdose. *Lancet* 1982; ii: 1218–19.
5. Miller ARO, Ingamells CJ. Gastrointestinal haemorrhage associated with an overdose of verapamil. *BMJ* 1984; 288: 1346.
6. Barrow PM, *et al.* Overdose of sustained-release verapamil. *Br J Anaesth* 1994; 72: 361–5.
7. Young AC, *et al.* Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. *Resuscitation* 2009; 80: 591–3.
8. Buckley CD, Aronson JK. Prolonged half-life of verapamil in a case of overdose: implications for therapy. *Br J Clin Pharmacol* 1995; 39: 680–3.
9. Stehle G, *et al.* Cardiogenic shock associated with verapamil in a patient with liver cirrhosis. *Lancet* 1990; 336: 1079.

Precautions

Verapamil is contra-indicated in hypotension, cardiogenic shock, marked bradycardia, and uncompensated heart failure. It is also contra-indicated in second- or third-degree AV block, and in the sick-sinus syndrome, unless a pacemaker is fitted. There is an increased incidence of adverse cardiac effects in patients with hypertrophic cardiomyopathy. In patients with atrial flutter or fibrillation and an accessory pathway with anterograde conduction, for example Wolff-Parkinson-White syndrome, verapamil may induce severe ventricular tachycardia and it is usually contra-indicated in such patients.

Special care is required in using verapamil as an antiarrhythmic in infants as they may be more susceptible to verapamil-induced arrhythmias.

Doses of verapamil should be reduced in patients with hepatic impairment.

Sudden withdrawal of verapamil might be associated with exacerbation of angina.

Breast feeding. Verapamil concentrations in breast milk similar to those found in plasma have been reported[1] in a woman taking verapamil 80 mg four times daily. The maximum concentration measured in breast milk was 300 nanograms/mL. However, the average concentration in milk in another woman[2] taking 80 mg three times daily was 23% of that in serum. The serum concentration of verapamil in the breast-fed child was 2.1 nanograms/mL during treatment and undetectable 38 hours after the last maternal dose. In another patient[3] taking the same dose, the average steady-state concentrations of verapamil and norverapamil in milk were, respectively, 60% and 16% of the concentration in plasma, with the ratio between milk and plasma varying during a dosage interval. It was esti-

mated that the infant received less than 0.01% of the mother's dose, and no verapamil or norverapamil could be detected in the plasma of the infant. No adverse effects have been seen in breast-feeding infants, and the American Academy of Pediatrics considers[4] that verapamil is therefore usually compatible with breast feeding.

1. Inoue H, *et al.* Level of verapamil in human milk. *Eur J Clin Pharmacol* 1984; 26: 657–8.
2. Andersen HJ. Excretion of verapamil in human milk. *Eur J. Clin Pharmacol* 1983; 25: 279–80.
3. Anderson P, *et al.* Verapamil and norverapamil in plasma and breast milk during breast feeding. *Eur J Clin Pharmacol* 1987; 31: 625–7.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 10/07/07)

Muscular disorders. Sudden respiratory failure was believed to have been precipitated by intravenous verapamil therapy in a patient with Duchenne's muscular dystrophy.[1]

1. Zalman F, *et al.* Acute respiratory failure following intravenous verapamil in Duchenne's muscular dystrophy. *Am Heart J* 1983; 105: 510–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies verapamil as probably porphyrinogenic; it should be prescribed only for compelling reasons and precautions should be considered in all patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Wolff-Parkinson-White Syndrome. Patients with atrial flutter or fibrillation and an accessory pathway, such as those with Wolff-Parkinson-White syndrome, may be at increased risk of developing ventricular tachycardia if AV-blocking drugs such as verapamil are used, since conduction across the anomalous pathway may be increased. Ventricular fibrillation and severe hypotension have been reported[1] after the use of intravenous verapamil 5 to 10 mg in patients with the Wolff-Parkinson-White syndrome.

1. McGovern B, *et al.* Precipitation of cardiac arrest by verapamil in patients with Wolff-Parkinson-White syndrome. *Ann Intern Med* 1986; 104: 791–4.

Interactions

Verapamil should be used with caution with drugs that have antiarrhythmic or beta-blocking effects; the use of intravenous verapamil with a beta blocker is especially hazardous (see below). Verapamil is extensively metabolised in the liver and interactions may occur with drugs that inhibit or enhance hepatic metabolism. Grapefruit juice may cause increased plasma concentrations of verapamil. Verapamil can itself affect the pharmacokinetics of other drugs, particularly by inhibition of the cytochrome P450 isoenzyme CYP3A4 and by effects on P-glycoprotein. Drugs affected include carbamazepine, ciclosporin, digoxin, midazolam, simvastatin, and theophylline; the plasma concentration of alcohol may also be increased. For details of these interactions, see under the individual drug monographs.

Analgesics. For a possible interaction of verapamil with *aspirin*, see under Antiplatelets, below.

Antiarrhythmics. Verapamil may have pharmacodynamic and pharmacokinetic interactions with other antiarrhythmics. Cardiogenic shock and asystole occurred in 2 patients receiving *flecainide* when verapamil was added to their therapy.[1] Verapamil given intravenously has been reported to cause severe hypotension in patients also receiving oral *quinidine*;[2] both drugs block alpha-adrenoceptors and verapamil may also increase the plasma concentration of quinidine.

1. Buss J, *et al.* Asystole and cardiogenic shock due to combined treatment with verapamil and flecainide. *Lancet* 1992; 340: 546.
2. Maisel AS, *et al.* Hypotension after quinidine plus verapamil: possible additive competition at alpha-adrenergic receptors. *N Engl J Med* 1985; 312: 167–70.

Antibacterials. Acute verapamil toxicity manifested by complete heart block has been reported in a patient after the use of *ceftriaxone* and *clindamycin*.[1] Displacement of verapamil from binding sites was postulated as the probable mechanism of action. *Rifampicin* is an enzyme-inducing drug and has been reported[2,3] to reduce plasma-verapamil concentrations. A verapamil dose of 1.92 g was required to control supraventricular tachycardia in a patient also taking rifampicin[2] and when rifampicin was withdrawn the plasma-verapamil concentration 9 days later was almost four times higher. A patient taking propranolol and verapamil developed symptomatic bradycardia a few days after starting treatment with *clarithromycin* and on another occasion after starting treatment with *erythromycin*.[4] Inhibition of verapamil metabolism by the antibacterials was proposed as the mechanism for the interaction. A further case of severe hypotension and bradycardia has also been reported[5] in a patient shortly after beginning therapy with clarithromycin and verapamil, and similar effects were seen[6] in a patient 2 days after starting *telithromycin*. A case of complete heart block has been reported[7] in a patient aged 79 taking verapamil, one week after erythromycin was added to her therapy, probably due to mutual inhibition of hepatic metabolism of both drugs.

1. Kishore K, *et al.* Acute verapamil toxicity in a patient with chronic toxicity: possible interaction with ceftriaxone and clindamycin. *Ann Pharmacother* 1993; 27: 877–80.
2. Rahn KH, *et al.* Reduction of bioavailability of verapamil by rifampin. *N Engl J Med* 1985; 312: 920–1.
3. Barbarash RA. Verapamil-rifampin interaction. *Drug Intell Clin Pharm* 1985; 19: 559–60.
4. Steenbergen JA, Stauffer VL. Potential macrolide interaction with verapamil. *Ann Pharmacother* 1998; 32: 387–8.
5. Kaeser YA, *et al.* Severe hypotension and bradycardia associated with verapamil and clarithromycin. *Am J Health-Syst Pharm* 1998; 55: 2417–18.
6. Reed M, *et al.* Verapamil toxicity resulting from a probable interaction with telithromycin. *Ann Pharmacother* 2005; 39: 357–60.
7. Goldschmidt N, *et al.* Compound cardiac toxicity of oral erythromycin and verapamil. *Ann Pharmacother* 2001; 35: 1396–9.

Antiepileptics. *Phenobarbital* is a hepatic enzyme-inducing drug and has been reported[1] to increase the clearance of oral and intravenous verapamil and to reduce oral bioavailability in healthy subjects. Plasma protein binding of verapamil was also reduced. Dosage adjustment of verapamil may be needed in patients also taking phenobarbital. Marked reduction in verapamil concentrations has also occurred with *phenytoin*.[2]

For a report of neurotoxicity in patients given verapamil with *carbamazepine*, see Calcium-channel Blockers, under Interactions of Carbamazepine, p. 517.2.

1. Rutledge DR, *et al.* Effects of chronic phenobarbital on verapamil disposition in humans. *J Pharmacol Exp Ther* 1988; 246: 7–13.
2. Woodcock BG, *et al.* A reduction in verapamil concentrations with phenytoin. *N Engl J Med* 1991; 325: 1179.

Antiplatelet drugs. Calcium-channel blockers can inhibit platelet function (see Effects on the Blood under Adverse Effects of Nifedipine, p. 1450.3). Use of verapamil and *aspirin* in an 85-year-old man was considered to be the cause of ecchymoses and retroperitoneal bleeding that developed about 3 weeks after starting treatment with the combination.[1]

1. Verzino E, *et al.* Verapamil-aspirin interaction. *Ann Pharmacother* 1994; 28: 536–7.

Benzodiazepines. For the effects of verapamil on the pharmacokinetics of *midazolam*, see Calcium-channel Blockers, p. 1069.3.

Beta blockers. Oral verapamil and beta blockers have been used together in the treatment of angina and hypertension but both drugs have cardiodepressant activity and the combination, if used at all, must be used with extreme caution; bradycardia, heart block, and left ventricular failure have been reported.[1-4] Bradycardia has also been reported[5] in a patient treated with *timolol* eye drops and oral verapamil. Patients with severe ischaemic heart disease or heart failure are particularly at risk.[6] The risks are increased with intravenous verapamil, and it has been suggested[6] that treatment with beta blockers should be stopped at least 24 hours before giving verapamil by this route; the interaction is particularly hazardous when both verapamil and beta blockers are given intravenously, and such combinations are not recommended.

Verapamil may also affect the pharmacokinetics of some beta blockers (see Calcium-channel Blockers, under Interactions of Beta Blockers, p. 1322.1).

1. Eisenberg JNH, Oakley GDG. Probable adverse interaction between oral metoprolol and verapamil. *Postgrad Med J* 1984; 60: 705–6.
2. Hutchison SJ, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; 289: 659–60.
3. Findlay IN, *et al.* β blockers and verapamil: a cautionary tale. *BMJ* 1984; 289: 1074.
4. McGourty JC, Silas JH. β blockers and verapamil: a cautionary tale. *BMJ* 1984; 289: 1624.
5. Pringle SD, MacEwen CJ. Severe bradycardia due to interaction of timolol eye drops and verapamil. *BMJ* 1987; 294: 155–6.
6. McInnes GT. Interactions that matter: calcium blockers. *Prescribers' J* 1988; 28: 60–4.

Calcium salts. Calcium salts antagonise the pharmacological response to verapamil and other calcium-channel blockers and are given intravenously to treat their adverse effects (see Treatment of Adverse Effects under Nifedipine, p. 1452.3). Recurrence of atrial fibrillation has occurred[1] during maintenance verapamil treatment when calcium adipinate and calciferol were given orally.

1. Bar-Or D, Yoel G. Calcium and calciferol antagonise effect of verapamil in atrial fibrillation. *BMJ* 1981; 282: 1585–6.

Everolimus. For the effect of verapamil on everolimus, see p. 1963.2.

General anaesthetics. For a recommendation that verapamil should not be used in patients anaesthetised with *halothane* or *enflurane*, see under Interactions of Diltiazem, p. 1361.3.

Histamine H_2-antagonists. Studies in healthy subjects using single doses of verapamil after pretreatment with *cimetidine* for up to 8 days have produced conflicting results. The pharmacokinetics of intravenous verapamil were unaltered by cimetidine in some studies,[1,2] but a 21% reduction in clearance and a 50% increase in the elimination half-life were also reported.[3] The pharmacokinetics of oral verapamil were unchanged in one study[2] but two others[1,4] reported a significant increase in bioavailability. Although one of these studies[1] found the interaction had no clinical effects, the other[4] reported an increased clinical effect in 5 of 6 subjects. The interaction with cimetidine appears to be stereoselective since the oral bioavailability of the *S*-enantiomer increased by 35% and that of the *R*-enantiomer by 15%.[4] The clinical significance of this interaction in patients and during long-term verapamil treatment is unknown, but cimetidine should be used with caution in patients receiving verapamil.

1. Smith MS, *et al.* Influence of cimetidine on verapamil kinetics and dynamics. *Clin Pharmacol Ther* 1984; 36: 551–4.
2. Abernethy DR, *et al.* Lack of interaction between verapamil and cimetidine. *Clin Pharmacol Ther* 1985; 38: 342–9.
3. Loi C-M, *et al.* Effect of cimetidine on verapamil disposition. *Clin Pharmacol Ther* 1985; 37: 654–7.
4. Mikus G, *et al.* Interaction of verapamil and cimetidine: stereochemical aspects of drug metabolism, drug disposition and drug action. *J Pharmacol Exp Ther* 1990; 253: 1042–8.

Lithium. Verapamil may have effects on neuromuscular function (see Extrapyramidal Disorders, p. 1524.2) and neurotoxicity has occurred[1-4] in patients receiving lithium after the addition of verapamil to their therapy, despite serum-lithium concentrations (where reported[1,2,4]) remaining in the therapeutic range. Verapamil has also been reported to decrease serum-lithium concentrations.[5]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; 26: 717–19.
2. Price WA, Shalley JE. Lithium-verapamil toxicity in the elderly. *J Am Geriatr Soc* 1987; 35: 177–8.
3. Helmuth D, *et al.* Choreoathetosis induced by verapamil and lithium treatment. *J Clin Psychopharmacol* 1989; 9: 454–5.
4. Wright BA, Jarrett DB. Lithium and calcium channel blockers: possible neurotoxicity. *Biol Psychiatry* 1991; 30: 635–6.
5. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; 108: 1378–80.

St John's wort. A study in healthy subjects[1] found that repeated doses of St John's wort significantly reduced the plasma concentrations of both the *R*- and *S*-isomers of verapamil, probably due to induction of the cytochrome P450 isoenzyme CYP3A4.

1. Tannergren C, *et al.* St John's wort decreases the bioavailability of *R*- and *S*-verapamil through induction of the first-pass metabolism. *Clin Pharmacol Ther* 2004; 75: 298–309.

Statins. A small crossover study[1] in healthy subjects suggested that oral *lovastatin* 20 mg produced marked increases in exposure and peak plasma concentrations of verapamil (about 60 and 30% respectively); the total increase in verapamil bioavailability was calculated at around 76%, and was thought to be due to inhibition of P-glycoprotein and first-pass metabolism of verapamil.

For mention of the effects of verapamil on a statin, see under Simvastatin, p. 1495.2.

1. Choi D-H, *et al.* Pharmacokinetic interaction between oral lovastatin and verapamil in healthy subjects: role of P-glycoprotein inhibition by lovastatin. *Eur J Clin Pharmacol* 2010; 66: 285–90.

Theophylline. For the effects of verapamil on the pharmacokinetics of theophylline, see Calcium-channel Blockers, p. 1235.3.

Tolvaptan. For the effect of verapamil on tolvaptan concentrations, see p. 2633.1.

Pharmacokinetics

Verapamil is about 90% absorbed from the gastrointestinal tract, but is subject to considerable first-pass metabolism in the liver and the bioavailability is only about 20%.

Verapamil has bi- or tri-phasic elimination kinetics and is reported to have a terminal plasma half-life of 2 to 8 hours after a single oral dose or after intravenous dosage. With repeated oral doses half-life increases to 4.5 to 12 hours. Verapamil acts within 5 minutes when given intravenously and within 1 to 2 hours when given orally; peak plasma concentrations occur 1 to 2 hours after an oral dose. There is considerable interindividual variation in plasma concentrations.

Verapamil is about 90% bound to plasma proteins. It is extensively metabolised in the liver to at least 12 metabolites of which norverapamil has been shown to have some activity. About 70% of a dose is excreted by the kidneys in the form of its metabolites but about 16% is excreted in the bile into the faeces. Less than 4% is excreted

unchanged. Verapamil crosses the placenta and is distributed into breast milk.

Reviews.

1. Hamann SR, *et al.* Clinical pharmacokinetics of verapamil. *Clin Pharmacokinet* 1984; 9: 26–41.
2. Kelly JG, O'Malley K. Clinical pharmacokinetics of calcium antagonists: an update. *Clin Pharmacokinet* 1992; 22: 416–35.
3. Kang D, *et al.* Population analyses of sustained-release verapamil in patients: effects of sex, race, and smoking. *Clin Pharmacol Ther* 2003; 73: 31–40.

The elderly. Studies[1-3] comparing the pharmacokinetics and pharmacodynamics of verapamil in elderly (61 years and older) and young subjects have found that clearance and elimination half-life are increased in older subjects, and increased plasma concentrations have also been reported. However, there may also be changes in the response to verapamil in older subjects that are not directly related to the plasma concentration.

1. Abernethy DR, *et al.* Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients: altered electrocardiographic and hypotensive responses. *Ann Intern Med* 1986; 105: 329–36.
2. Gupta SK, *et al.* Age and gender related changes in stereoselective pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *Br J Clin Pharmacol* 1995; 40: 325–31.
3. Abernethy DR, *et al.* Verapamil metabolite exposure in older and younger men during steady-state oral verapamil administration. *Drug Metab Dispos* 2000; 28: 760–5.

Metabolism. Verapamil is extensively metabolised in the liver to several metabolites, and several cytochrome P450 isoenzymes appear to be involved. An *in-vitro* study[1] has suggested that the main isoenzymes responsible for the metabolism of both enantiomers of verapamil are CYP3A4, CYP3A5, and CYP2C8, and that the same isoenzymes are involved in the further metabolism of norverapamil. However, since CYP2C8 generally makes up only a small part of the cytochrome P450 content of the liver, it was considered that this would have little significance for potential drug interactions. In contrast to some previous reports, the isoenzymes CYP1A2 and CYP2C9 were not found to be involved to any great extent.

1. Tracy TS, *et al.* Cytochrome P450 isoforms involved in metabolism of the enantiomers of verapamil and norverapamil. *Br J Clin Pharmacol* 1999; 47: 545–52.

Stereospecificity. Verapamil is used as a racemic mixture. It has been shown[1] that *S*-verapamil is 3.3 times more potent than the racemic mixture and 11 times more potent than *R*-verapamil. Thus it was concluded that the cardiac effects of verapamil are related not to the total plasma-verapamil concentration but to the concentration of the *S*-isomer, and conventional plasma concentration monitoring will be of little value in establishing therapeutic plasma concentrations during multiple oral dosing.

A series of studies have been carried out to determine whether differences in the pharmacokinetics of the *R*- and *S*-isomers of verapamil could account for the differences in the plasma concentration-response curve after oral and intravenous doses. When given intravenously, there were pronounced differences in the pharmacokinetics and protein binding of the 2 isomers;[2] the volume of distribution and total systemic clearance of *S*-verapamil were much higher than those of the *R*-isomer although the terminal half-life was similar. After oral doses of a mixture of *R*- and *S*-verapamil, plasma concentrations of the *R*-isomer were found to be substantially higher than those of the more potent *S*-isomer,[3] suggesting stereospecific first-pass hepatic metabolism and accounting for the apparent lower potency of verapamil when given orally. The proportion of *S*-isomer also depends on the oral formulation; modified-release formulations produce lower proportions of *S*-isomer in plasma than conventional formulations.[4]

1. Echizen H, *et al.* Effects of d,l-verapamil on atrioventricular conduction in relation to its stereoselective first-pass metabolism. *Clin Pharmacol Ther* 1985; 38: 71–6.
2. Eichelbaum M, *et al.* Pharmacokinetics of (+)-, (-)- and (±)-verapamil after intravenous administration. *Br J Clin Pharmacol* 1984; 17: 453–8.
3. Vogelgesang B, *et al.* Stereoselective first-pass metabolism of highly cleared drugs: studies of the bioavailability of L- and D-verapamil examined with a stable isotope technique. *Br J Clin Pharmacol* 1984; 18: 733–40.
4. Karim A, Piergies A. Verapamil stereoisomerism: enantiomeric ratios in plasma dependent on peak concentrations, oral input rate, or both. *Clin Pharmacol Ther* 1995; 58: 174–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Isoptino; Veral; Verapal; *Austral.*: Anpec Cordilox; Isoptin; Veracaps; Verahexal†; *Austria*: Isoptin; Verapabene; Veroptinstada; *Belg.*: Isoptine; Lodixal; *Braz.*: Cordilat; Coronaril; Dilacor; Dilacoron; Multicor†; Neo Verpamil; Vasoton; Veramil; Verapress†; Veraval; *Canad.*: Apo-Verap; Covera†; Isoptin; Novo-Veramil; Nu-Verap; Verelan; *Chile*: Cardiolen; Isoptina; Presocor†; *China*: Ao Di Mai Er (奥地迈尔); Ba Ping Te Jia (巴平特佳); Gai Heng (盖衡); Isoptin (异搏定); Novopressan (诺富生); Shida (释达); *Cz.*: Isoptin; Lekoptin; Verahexal; Verogalid; *Denm.*: Hexasoptin; Isoptin; Veraloc; *Fin.*: Isoptin; Vermin†; Verpamil; *Fr.*: Isoptine; *Ger.*: Falicard; Isoptin; Vera-Lich†; Vera; Verabeta; Veragamma; Verahexal†; Veramex†; Veranorm†; Verasal†; Veroptinstada†; *Gr.*: Brovicarpine; Elanver; Isoptin; Ranil; *Hong Kong*: Anpec†; Apo-Verap; Isoptin; Verpamil†; *Hung.*: Chinopamil; Isoptin; *India*: Calaptin; Veramil; *Indon.*: Cardiover; Isoptin; *Irl.*: Isoptin; Veramil; Verap; Verisop; *Israel*: Ikacor; Ikapress; Verapress; *Ital.*: Cardinorm; Isoptin; Kata; Veraptin; *Jpn*: Vasolan; *Malaysia*: Akilen†; Isoptin; Verpamil; *Mex.*: Cronovera; Dilacoran; Europave†; Serriten; Vepiltax; Veraken; Verdilac; *Neth.*: Isoptin; *Norw.*: Isoptin; Verakard; *NZ*: Isoptin; Verpamil; *Philipp.*: Isoptin; Verelan; *Pol.*: Isoptin; Lekoptin†; Novo-Veramil; Staveran; *Port.*: Fibrocard†; Isoptin; *Rus.*: Finoptin (Финоптин); Isoptin (Изоптин); Lekoptin (Лекоптин)†; Verogalid (Верогалид); Veromil (Веромил)†; *S.Afr.*: Calcicard; Isoptin; Ravamil; Vasomil; Verahexal; *Singapore*: Beaptin; Isoptin; Verpamil; *Spain*: Manidon; *Swed.*: Isoptin; *Switz.*: Flamon; Isoptin; Verapam†; *Thal.*: Caveril; Isoptin; Sopmil; Verapin†; Vermine; *Turk.*: Fibrocard; Isoptin; Ormil; Veroptin; *UK*: Cordilox; Half Securon; Securon; Univer; Verapress; Vertab; Zolvera; *Ukr.*: Finoptin (Финоптин); Lekoptin (Лекоптин); Veratard (Вератард); Verogalid (Верогалид); *USA*: Calan; Covera; Isoptin; Verelan; *Venez.*: Cronovera; Manidon; Veracor.

Multi-ingredient Preparations. *Austral.*: Tarka; *Austria*: Conlit; Veracapt; *Canad.*: Tarka; *Cz.*: Tarka; *Denm.*: Tarka; *Fr.*: Tarka; *Ger.*: Cordichin; Isoptin plus; Tarka; Veratide†; *Gr.*: Tarka; Ziaxel; *Hong Kong*: Tarka; *Hung.*: Tarka; *Indon.*: Tarka; *Ital.*: Tarka; *Mex.*: Tarka; *Neth.*: Tarka; Ziaxel; *NZ*: Ziaxel†; *Philipp.*: Tarka; *Pol.*: Tarka; *Port.*: Tarka; Ziaxel; *Rus.*: Tarka (Тарка); *S.Afr.*: Tarka; *Spain*: Tarka; Tricen†; *Swed.*: Tarka†; *Switz.*: Tarka; *Turk.*: Tarka; *UK*: Tarka; *Ukr.*: Tarka (Тарка); *USA*: Tarka; *Venez.*: Tarka.

Pharmacopoeial Preparations

BP 2014: Prolonged-release Verapamil Capsules; Prolonged-release Verapamil Tablets; Verapamil Injection; Verapamil Tablets;

USP 36: Verapamil Hydrochloride Extended-Release Capsules; Verapamil Hydrochloride Extended-release Tablets; Verapamil Hydrochloride Injection; Verapamil Hydrochloride Oral Solution; Verapamil Hydrochloride Oral Suspension; Verapamil Hydrochloride Tablets.

Vernakalant Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de vernakalant; RSD-1235; Vernakalant, Chlorhydrate de; Vernakalanti Hydrochloridum; Вернакаланта Гидрохлорид.

(3*R*)-1-[(1*R*,2*R*)-2-[2-(3,4-dimethoxyphenyl)ethoxy]cyclohexyl]pyrrolidin-3-ol hydrochloride.

$C_{20}H_{31}NO_4$,HCl=385.9

CAS — 794466-70-9 (vernakalant); 748810-28-8 (vernakalant hydrochloride).

ATC — C01BG11.

ATC Vet — QC01BG11.

UNII — 7G4J1ZD9UQ.

NOTE. The name Kynapid has been used as a trademark for vernakalant hydrochloride.

Uses and Administration

Vernakalant hydrochloride is an antiarrhythmic drug used for the rapid conversion of recent-onset atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1). It acts by selective inhibition of atrial sodium and potassium repolarising currents and can therefore be classified as both a class I and class III antiarrhythmic.

Vernakalant hydrochloride may be given to non-surgical patients up to 7 days after onset of atrial fibrillation, or to surgical patients up to 3 days after onset. It is given by intravenous infusion at a dose of 3 mg/kg (maximum dose of 339 mg) over 10 minutes. If conversion to sinus rhythm does not occur within 15 minutes of this infusion, a second 10-minute infusion of 2 mg/kg (maximum dose of 226 mg) may be given. A cumulative dose of 5 mg/kg per 24 hours should not be exceeded. If conversion to sinus rhythm occurs during either infusion, the infusion should be continued to completion.

An oral formulation is also under investigation.

References.

1. Roy D, *et al.* A randomized, controlled trial of RSD1235, a novel anti-arrhythmic agent, in the treatment of recent onset atrial fibrillation. *J Am Coll Cardiol* 2004; 44: 2355–61.
2. Cheng JWM. Vernakalant in the management of atrial fibrillation. *Ann Pharmacother* 2008; 42: 533–42.
3. Kozlowski D, *et al.* Vernakalant hydrochloride for the treatment of atrial fibrillation. *Expert Opin Invest Drugs* 2009; 18: 1929–37.
4. Kowey PR, *et al.* Atrial Arrhythmia Conversion Trial Investigators. Vernakalant hydrochloride for the rapid conversion of atrial fibrillation after cardiac surgery: a randomized, double-blind, placebo-controlled trial. *Circ Arrhythm Electrophysiol* 2009; 2: 652–9.
5. Pinnin M. Vernakalant: A novel agent for the termination of atrial fibrillation. *Am J Health-Syst Pharm* 2010; 67: 1157–64.

Adverse Effects

Vernakalant hydrochloride often causes bradycardia, particularly at the time of conversion to sinus rhythm. Atrial flutter is also common, but usually converts to sinus rhythm with ongoing infusion. Less common cardiovascular adverse effects include heart block, ventricular tachycardia, and prolongation of the QRS complex or QT interval.

Other adverse effects include sneezing, taste disturbances, hypotension, dry mouth, hyperhidrosis, and pruritus.

Precautions

Vernakalant is contra-indicated in those with severe aortic stenosis, a systolic blood pressure of less than 100 mmHg, prolonged QT interval, severe bradycardia, sinus node dysfunction, or second- or third-degree heart block in the absence of a pacemaker. It should not be used within 4 hours of intravenous administration of a class I or III antiarrhythmic, nor within 30 days of an acute coronary syndrome. It is contra-indicated in moderate or severe heart failure (NYHA class III or IV), but may be used with caution in stable class I or II heart failure.

The infusion should be stopped if clinically significant bradycardia, hypotension, or ECG changes occur.

Interactions

Vernakalant should be used with caution in patients taking other antiarrhythmic drugs (see also Precautions, above). Vernakalant may prolong the QT interval, and there is a theoretical risk of serious ventricular arrhythmias when it is given with other QT-interval-prolonging drugs.

Pharmacokinetics

The pharmacokinetics of vernakalant are linear. It undergoes *O*-demethylation in the liver via the cytochrome P450 isoenzyme CYP2D6, followed by glucuronide conjugation. It has a mean elimination half-life of 3 hours in extensive metabolisers, and 5.5 hours in poor metabolisers.

References.

1. Mao ZL, *et al.* Pharmacokinetics of novel atrial-selective antiarrhythmic agent vernakalant hydrochloride injection (RSD1235): influence of CYP2D6 expression and other factors. *J Clin Pharmacol* 2009; 49: 17–2[illegible].

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Brinavess; *Cz.*: Brinaves; *Denm.*: Brinavess; *Ger.*: Brinavess; *Gr.*: Brinavess; *Irl.*: Brinavess; *Israel*: Brinavess; *Neth.*: Brinavess; *Norw.*: Brinavess; *Pol.*: Brinavess; *Port.*: Brinavess; *Spain*: Brinavess; *Swed.*: Brinaves; *Switz.*: Brinavess.

Vorapaxar *(USAN, rINN)*

SCH-530348 (vorapaxar sulfate); Vorapaxarum; Ворапаксар.

Ethyl [(1*R*,3a*R*,4a*R*,6*R*,8a*R*,9*S*,9a*S*)-9-[(1*E*)-2-[5-(3-fluorophenyl)pyridin-2-yl]ethen-1-yl]-1-methyl-3-oxododecahydronaphtho[2,3-*c*]furan-6-yl]carbamate.

$C_{29}H_{33}FN_2O_4$=492.6

CAS — 618385-01-6 (vorapaxar); 705260-08-8 (vorapaxar sulfate).

UNII — ZCE93644N2.

NOTE. Vorapaxar Sulfate is *USAN*.

Profile

Vorapaxar is a protease activated receptor-1 (PAR-1) antagonist that blocks thrombin-mediated platelet activation. It is given orally and is under investigation for the prevention and treatment of thrombosis; however, there have been concerns about a possible increased risk of stroke.

References.

1. Leonardi S, *et al.* Thrombin receptor antagonists for the treatment of atherothrombosis: therapeutic potential of vorapaxar and E-5555. *Drugs* 2010; 70: 1771–83.

Warfarin *(BAN, rINN)*

Coumaphène; Hydroxyoxophenylbutylcoumarin; Varfarilini; Varfarin; Varfarina; Warfarina; Warfarine; Warfarinum; Warfaryna; Варфарин.

(*RS*)-4-Hydroxy-3-(3-oxo-1-phenylbutyl)coumarin.

$C_{19}H_{16}O_4$=308.3

CAS — 81-81-2.

ATC — B01AA03.

ATC Vet — QB01AA03.

UNII — 5Q7ZVV76EI.

Warfarin Potassium *(BANM, rINNM)*

Kalii Warfarinum; Potassium Warfarin; Warfarina potasica; Warfarine Potassique; Warfarinum Kalicum; Калия Варфарин.

$C_{19}H_{15}KO_4$=346.4

CAS — 2610-86-8.

ATC — B01AA03.

ATC Vet — QB01AA03.
UNII — I47IU4FOCO.

Pharmacopoeias. In *Jpn.*

Warfarin Sodium (BANM, rINNM)

Natrii Warfarinum; Sodium Warfarin; Varfariininatrium; Varfarin Sodyum; Varfarino natrio druska; Warfarin-Natrium; Warfarin sodná sůl; Warfarina sódica; Warfarine Sodique; Warfarinnatrium; Warfarin-nátrium; Warfarinum natricum; Натрий Варфарин.

$C_{19}H_{15}NaO_4$=330.3
CAS — 129-06-6.
ATC — B01AA03.
ATC Vet — QB01AA03.
UNII — 6153CWM0CL.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate. *Eur.* has a separate monograph for warfarin sodium clathrate (see below).

Ph. Eur. 8: (Warfarin Sodium). A white or almost white, hygroscopic, amorphous powder. Very soluble in water and in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

USP 36: (Warfarin Sodium). A white, odourless, amorphous solid or a crystalline clathrate which is discoloured by light. Very soluble in water; freely soluble in alcohol; very slightly soluble in chloroform and in ether. A 1% solution in water has a pH of 7.2 to 8.3. Protect from light.

Adsorption. Studies carried out for periods of 24 hours to 3 months found some adsorption of warfarin sodium by PVC when dissolved in 0.9% sodium chloride solution[1,2] or in 5% glucose solution.[3] In one of these studies,[1] adsorption was decreased by buffering the solution from its initial pH of 6.7 to a pH of 7.4. The second study[2] found no adsorption onto polyethylene-lined or glass infusion containers.

1. Kowaluk EA, *et al.* Interactions between drugs and polyvinyl chloride infusion bags. *Am J Hosp Pharm* 1981; 38: 1308–14.
2. Martens HJ, *et al.* Sorption of various drugs in polyvinyl chloride, glass, and polyethylene-lined infusion containers. *Am J Hosp Pharm* 1990; 47: 369–73.
3. Moorhatch P, Chiou WL. Interactions between drugs and plastic intravenous fluid bags: part I: sorption studies on 17 drugs. *Am J Hosp Pharm* 1974; 31: 72–8.

Incompatibility. Solutions of warfarin sodium have been reported to be incompatible with adrenaline hydrochloride, amikacin sulfate, metaraminol tartrate, oxytocin, promazine hydrochloride, and tetracycline hydrochloride. Visual incompatibility has been reported[1] with solutions of warfarin sodium mixed with solutions of aminophylline, bretylium tosilate, ceftazidime, cimetidine hydrochloride, ciprofloxacin lactate, dobutamine hydrochloride, esmolol hydrochloride, gentamicin sulfate, labetalol hydrochloride, metronidazole hydrochloride, or vancomycin hydrochloride. Haze was also reported after 24 hours with sodium chloride 0.9%.

1. Bahal SM, *et al.* Visual compatibility of warfarin sodium injection with selected medications and solutions. *Am J Health-Syst Pharm* 1997; 54: 2599–2600.

Warfarin Sodium Clathrate (BANM)

Varfariininatriumklatraatti; Varfarino natrio druskos klatratas; Warfarin-Natrium-Clathrat; Warfarin sodná sůl klatrát; Warfarina sódica, clatrato de; Warfarine sodique clathrate; Warfarinnatriumklatrat; Warfarin-nátrium-klatrát; Warfarinum Natricum Clathratum.

The clathrate of warfarin sodium with isopropyl alcohol in the molecular proportions 2 to 1 respectively.
ATC — B01AA03.
ATC Vet — QB01AA03.

NOTE. The use of the term warfarin sodium in *Martindale* should generally be taken to include the sodium clathrate. Until 1991 the BP, like the USP, allowed the use of either warfarin sodium or warfarin sodium clathrate in the definition of warfarin sodium.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin., *Int.*, and *US* permit either warfarin sodium or warfarin sodium clathrate.

Ph. Eur. 8: (Warfarin Sodium Clathrate). A white or almost white, crystalline powder. Very soluble in water; freely soluble in alcohol; soluble in acetone; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 7.6 to 8.6. Store in airtight containers. Protect from light.

Warfarin sodium clathrate contains about 92% of warfarin sodium.

Uses and Administration

Warfarin is a coumarin anticoagulant used in the treatment and prophylaxis of thromboembolic disorders (p. 1273.2). It acts by depressing the hepatic vitamin K-dependent synthesis of coagulation factors II (prothrombin), VII, IX, and X, and of the anticoagulant protein C and its cofactor protein S. For an explanation of the coagulation cascade, see Haemostasis and Fibrinolysis, p. 1124.3. Since warfarin acts indirectly, it has no effect on existing clots. Also as the coagulation factors involved have half-lives ranging from 6 to 60 hours, several hours are required before an effect is seen. A therapeutic effect is usually apparent by 24 hours, but the peak effect may not be achieved until 2 or 3 days after a dose; the overall effect may last for 5 days.

Warfarin is used in the prevention and treatment of venous thromboembolism (deep-vein thrombosis and pulmonary embolism, p. 1274.1). If an immediate effect on blood coagulation is required, heparin should be given intravenously or subcutaneously to cover at least the first 5 days. Warfarin therapy may be begun with, or shortly after, initial heparin treatment. Warfarin is also used for the prevention of systemic thromboembolism and ischaemic stroke in some patients with atrial fibrillation (p. 1266.1), prosthetic heart valves (see Valvular Heart Disease, p. 1264.3), or who have suffered a myocardial infarction (p. 1257.1). It may also have a role in the prevention of myocardial infarction and in the management of stroke or transient ischaemic attacks (p. 1269.2). Antiplatelet drugs may be given concomitantly.

Warfarin may be used as a rodenticide, but resistance is common in *mice* and is developing in *rats*.

Administration and dosage. Warfarin is usually given orally but is equally effective given intravenously. Dosage must be determined individually as discussed below under Control of Anticoagulant Therapy. When rapid anticoagulation is required, an initial dose of warfarin sodium 10 mg may be given on the first day, although in many cases an initial dose of 5 mg daily is adequate; initial doses of less than 5 mg daily may be used in elderly patients and in those at increased risk of bleeding (see Precautions, p. 1529.2). Subsequent doses depend on the results of coagulation tests, but maintenance doses usually range from 3 to 9 mg daily. If necessary the same dose may be given by slow intravenous injection. Doses of warfarin sodium should be given at the same time each day. Theoretically, stopping warfarin abruptly may result in rebound hypercoagulability with risk of thrombosis. Therefore some clinicians have tailed off long-term treatment over several weeks. However, small studies suggest that a hypercoagulable state may persist for 8 to 9 weeks, regardless of the strategy used for stopping warfarin. The *American College of Chest Physicians* also considers that gradually stopping therapy may be confusing and inconvenient for the patient, and suggests that treatment may be stopped abruptly. Anticoagulant treatment booklets should be carried by patients.

Warfarin has also been given as the potassium salt; warfarin-deanol has been tried.

Control of oral anticoagulant therapy. Treatment with oral anticoagulants must be monitored to ensure that the dose is providing the required effect on the vitamin-K-dependent clotting factors; too small a dose provides inadequate anticoagulation, too large a dose puts the patient at risk of haemorrhage. This monitoring is commonly carried out by checking the clotting property of the patient's plasma using a suitable preparation of thromboplastin and a source of calcium. The time taken for the clot to form due to the effect of the thromboplastin preparation on prothrombin is known as the prothrombin time (PT). The prothrombin time ratio (PTR) is the prothrombin time of the patient's plasma divided by that for a standard plasma sample.

So that there is some consistency in prothrombin time ratios measured at different times or at different laboratories, it is now common practice for the manufacturer or control laboratory to calibrate their batches of thromboplastin against the international reference preparation. This calibration produces an international sensitivity index (ISI) appropriate to that thromboplastin. The laboratory measuring the clotting capacity of a sample of plasma is thus able to convert the prothrombin time ratio to an international normalised ratio (INR) using the sensitivity index through the formula

$$INR = PTR^{(ISI)}$$

Thus a PTR of 2.0 obtained with a thromboplastin with a declared ISI of 1.5 would be converted to an INR of 2.8. An INR is therefore equivalent to a PTR carried out using the primary international reference preparation of thromboplastin.

This method of standardisation has taken over from methods involving use of a standard reagent such as the British or Manchester comparative thromboplastin. Preparations of thromboplastin derived from *rabbit* brain have superseded or are superseding those from human brain because of the dangers of viral transmission; a recombinant human form is also available.

Recommended target values or ranges of INR for patients receiving anticoagulant treatment or cover for various conditions or procedures are given by the *British Society for Haematology* and the *American College of Chest Physicians*. These are given in Table 6, below. An INR within 0.5 units of the target value in the UK is generally considered satisfactory. In the USA it is recommended that the INR be maintained at the mid-level of the range. An INR less than 2.0 generally represents inadequate anticoagulation and an INR above 4.5 represents greater risk of haemorrhage.

Measurements should be carried out before treatment and then daily or on alternate days in the early stages of treatment. Once the dose has been established and the patient well stabilised the measurement can be made at greater but regular intervals, for example every 8 weeks; allowances should be made for any events that might influence the activity of the anticoagulant. Self-monitoring may be appropriate in some patients.

General references.

1. Le DT, *et al.* The international normalized ratio (INR) for monitoring warfarin therapy: reliability and relation to other monitoring methods. *Ann Intern Med* 1994; 120: 552–8.
2. Hirsh J, *et al.* American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. *Circulation* 2003; 107: 1692–1711. Also available at: http://circ.ahajournals.org/cgi/reprint/107/12/1692.pdf (accessed 25/02/05)
3. Fitzmaurice DA, *et al.* British Society of Haematology Taskforce for Haemostasis and Thrombosis. An evidence-based review and guidelines for patient self-testing and management of oral anticoagulation. *Br J Haematol* 2005; 131: 156–65. Correction. *ibid.* 2006; 132: 118. Also available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2005.05739.x/pdf (accessed 21/10/11)

Table 6. Recommended International Normalised Ratios (INR).

	INR	Condition or procedure
UK	2.5	Treatment of venous thromboembolism; thromboembolism associated with antiphospholipid syndrome; atrial fibrillation, mural thrombus, valvular heart disease, cardiomyopathy, and following myocardial infarction; acute peripheral arterial embolism proceeding to embolectomy; bioprosthetic heart valves.
	2.5 or 3.0	Cardioversion (higher INR may be appropriate before procedure); some mechanical prosthetic heart valves.
	3.5	Recurrence of venous thromboembolism when on warfarin; some mechanical prosthetic heart valves.
US	2.0 to 3.0	Treatment of venous thrombosis and pulmonary embolism; secondary prophylaxis of thromboembolism associated with antiphospholipid syndrome; patients with anterior myocardial infarction and left ventricular thrombus or high risk of thrombus; left ventricular dysfunction with thrombus; and for prophylaxis of systemic embolism in patients with atrial fibrillation (depending on risk factors for stroke), cardioversion, valvular heart disease, bioprosthetic heart valves or some mechanical prosthetic heart valves.
	2.5 to 3.5	Prophylaxis in patients with some mechanical prosthetic heart valves.

4. Keeling D, *et al.* British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin -fourth edition. *Br J Haematol* 2011; 154: 311–24. Correction. *ibid.*; 156: 150–2. Also available at: http://www.bcshguidelines.com/documents/warfarin_4th_ed.pdf (accessed 27/02/12)
5. Bloomfield HE, *et al.* Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. *Ann Intern Med* 2011; 154: 472–82.
6. Guyatt GH, *et al.* American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): 7S–47S. Correction. *ibid.*; 1129. [dose] Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/141253.pdf (accessed 21/09/12)
7. Holbrook A, *et al.* American College of Chest Physicians. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e152S–84S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112295.pdf (accessed 04/10/12)
8. Ageno W, *et al.* American College of Chest Physicians. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e44S–88S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112292.pdf (accessed 21/09/12)

Administration and dosage. Algorithms and guidelines have been developed for beginning anticoagulant therapy, based on the method of Fennerty *et al.*[1] Although a loading dose of 10 mg daily for 2 days (depending on the INR) has been widely used, lower doses may be more appropriate, especially in hospitalised patients at greater risk of over-anticoagulation. Studies[2–4] comparing warfarin loading doses of 5 and 10 mg found that for both groups a therapeutic INR in the range of 2.0 to 3.0 was reached in most patients by day 5 of treatment. Although a study of outpatients with venous thromboembolism[5] found that a therapeutic INR was achieved 1.4 days sooner with the larger loading dose, the nomogram used was not designed for inpatients.

In situations where rapid anticoagulation is not necessary, loading doses may not be required and treatment should begin with the estimated maintenance dose. Studies[6,7] have found that the maintenance dose decreases with age and is lower in women than in men, and lower initial doses are therefore recommended in the elderly. Regimens that have been suggested include warfarin in a dose of 4 mg daily for 3 days, then adjusted according to the INR,[8] or, for patients requiring anticoagulation prophylaxis, 2 mg daily for 2 weeks followed by weekly adjustment using an algorithm until the target INR is reached.

1. Fennerty A, *et al.* Flexible induction dose regimen for warfarin and prediction of maintenance dose. *BMJ* 1984; 288: 1268–70.
2. Harrison L, *et al.* Comparison of 5-mg and 10-mg loading doses in initiation of warfarin therapy. *Ann Intern Med* 1997; 126: 133–6.
3. Crowther MA, *et al.* Warfarin: less may be better. *Ann Intern Med* 1997; 127: 333.
4. Crowther MA, *et al.* A randomized trial comparing 5-mg and 10-mg warfarin loading doses. *Arch Intern Med* 1999; 159: 46–8.
5. Kovacs MJ, *et al.* Comparison of 10-mg and 5-mg warfarin initiation nomograms together with low-molecular-weight heparin for outpatient treatment of acute venous thromboembolism: a randomized, double-blind, controlled trial. *Ann Intern Med* 2003; 138: 714–19.
6. Singla DL, Morrill GB. Warfarin maintenance dosages in the very elderly. *Am J Health-Syst Pharm* 2005; 62: 1062–6.
7. Garcia D, *et al.* Warfarin maintenance dosing patterns in clinical practice: implications for safer anticoagulation in the elderly population. *Chest* 2005; 127: 2049–56.
8. Siguret V, *et al.* Initiation of warfarin therapy in elderly medical inpatients: a safe and accurate regimen. *Am J Med* 2005; 118: 137–42.

DOSE ADJUSTMENT IN SURGERY. The management of patients receiving vitamin K antagonist anticoagulants who require surgery has been reviewed.[1–4] Warfarin dose adjustment should take into account several factors including the risks of both perioperative arterial thromboembolism and bleeding associated with different types of surgery, as well as the initial indication for anticoagulation.

Guidance from the USA[2,4] suggests that where the risk of bleeding is low, warfarin may be continued uninterrupted; local haemostatic measures may be required for minor dental and dermatological procedures. When the bleeding risk is higher, warfarin should be stopped about 5 days before surgery. On the day before surgery, corrective oral vitamin K may be given if the INR is still above 1.5. Warfarin may be restarted about 12 to 24 hours after surgery and when there is adequate haemostasis. It has also been suggested that bridging anticoagulation should be used when warfarin is being withheld and there is a high risk of perioperative thromboembolism. A therapeutic dose regimen of low-molecular-weight heparin is generally used, starting about 3 days before surgery. The final pre-operative dose is given about 24 hours before surgery and treatment is restarted 48 to 72 hours after surgery depending on the bleeding risk and when haemostasis is achieved. If intravenous unfractionated heparin is used, it is stopped 4 to 6 hours before surgery. The role of bridging in moderate risk of perioperative thromboembolism is less clear, and its use depends on individual patient and surgical risk factors. When it is used, it might be considered possible to restart 24 hours after surgery.

In cases of emergency surgery,[2,3] warfarin is stopped and intravenous or oral vitamin K is given. Prothrombin complex concentrate is also used if anticoagulant reversal is needed in less than 24 hours. Fresh frozen plasma may be used if concentrate is not available, but the required dose may risk volume overload.

1. Thachil J, *et al.* Management of surgical patients receiving anticoagulation and antiplatelet agents. *Br J Surg* 2008; 95: 1437–48.
2. Douketis JD. Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. *Blood* 2011; 117: 5044–9.
3. Vang ML, *et al.* Urgent reversal of vitamin K antagonist therapy. *Acta Anaesthesiol Scand* 2011; 55: 507–16.
4. Douketis JD, *et al.* American College of Chest Physicians. Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e326S–50S. Correction. *ibid.*; 1129. [dose] Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112298.pdf (accessed 25/09/12)

Administration in children. Increasing numbers of infants and children are receiving anticoagulants for prophylaxis and treatment of thromboembolism. Doses of warfarin and therapeutic INR ranges have been adapted from adult therapy but cohort studies[1,2] of paediatric patients have found that warfarin requirements may be affected by several factors including age, and the use of infant formulas supplemented with vitamin K. Recommendations[3] for the use of oral anticoagulants in children have been published.

The *BNFC* suggests that neonates, children, and adolescents aged up to 18 years may be given an initial single oral dose of 200 micrograms/kg (maximum 10 mg) on the first day, adjusted over the next 3 days according to INR:

- INR < 1.4: 200 micrograms/kg (maximum 10 mg) once daily
- INR 1.4 to 3: 100 micrograms/kg (maximum 5 mg) once daily
- INR 3 to 3.5: 50 micrograms/kg (maximum 2.5 mg) once daily
- INR > 3.5: omit dose

The usual maintenance dose is 100 to 300 micrograms/kg once daily, adjusted according to INR. Up to 400 micrograms/kg may be needed in certain patients.

1. Tait RC, *et al.* Oral anticoagulation in paediatric patients: dose requirements and complications. *Arch Dis Child* 1996; 74: 228–31.
2. Streif W, *et al.* Analysis of warfarin therapy in pediatric patients: a prospective cohort study of 319 patients. *Blood* 1999; 94: 3007–14.
3. Monagle P, *et al.* American College of Chest Physicians. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e737S–801S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112308.pdf (accessed 21/09/12)

Catheters and cannulas. For mention of the use of oral anticoagulants to prevent thrombosis in patients with indwelling infusion devices, see Heparin Sodium, p. 1398.1.

Connective tissue and muscular disorders. Warfarin has been proposed to treat subcutaneous calcium deposition (calcinosis cutis) in patients with dermatomyositis, but its value is disputed, see Polymyositis and Dermatomyositis, p. 1611.1.

Adverse Effects

The major risk from warfarin therapy is of haemorrhage from almost any organ of the body with the consequent effects of haematomas as well as anaemia. Although good control of warfarin anticoagulation is essential in preventing haemorrhage, bleeding has occurred at therapeutic international normalised ratio (INR) values. In such cases the possibility of an underlying cause such as renal or alimentary tract disease should be investigated. Skin necrosis, and purple discoloration of the toes (due to cholesterol embolisation) have occasionally occurred. Hypersensitivity reactions are extremely rare. Other effects not necessarily associated with haemorrhage include alopecia, fever, nausea, vomiting, diarrhoea, skin reactions, jaundice, hepatic dysfunction, and pancreatitis.

Warfarin is a recognised teratogen. Given in the first trimester of pregnancy it can cause a fetal warfarin syndrome or warfarin embryopathy characterised by bone stippling (chondrodysplasia punctata) and nasal hypoplasia. CNS abnormalities may develop after use in any trimester but appear most likely when used in the second or third trimester. Use of warfarin during pregnancy has been associated with an increased rate of abortion and still-birth, although this may, in part, be the consequence of an underlying maternal condition. Use in the late stages of pregnancy is associated with fetal haemorrhage. Reported incidences of the above complications have varied considerably with maternal indications, doses, and treatment durations; analyses of reported cases have indicated that if a coumarin is taken throughout pregnancy, up to 30% of cases may result in spontaneous abortion or still-birth, and around 5% may result in an abnormal liveborn infant.

Effects on the blood. The incidence and risk of haemorrhage during long-term oral anticoagulation has been studied in patients in clinical studies[1,2] and in population-based studies.[1,3–7] The risk of bleeding was generally higher with more intense anticoagulation and in the presence of other risk factors, but the relationship with age was less clear. Some studies have shown higher rates of bleeding in elderly patients, but others have not; the risk of intracranial bleeding, however, does seem to be higher in the elderly.[2,6,7] Although cumulative risk of bleeding was related to duration of anticoagulation therapy, risk may be highest early in the course.[2]

Withdrawal of warfarin therapy may lead to rebound hypercoagulability and it has been suggested[8] that warfarin should be withdrawn gradually, although there is no clinical evidence to support this.

1. Reynolds MW, *et al.* Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and meta-analysis. *Chest* 2004; 126: 1938–45.
2. Schulman S, *et al.* Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (suppl): 257S–298S.
3. Gitter MJ, *et al.* Bleeding and thromboembolism during anticoagulant therapy: a population-based study in Rochester, Minnesota. *Mayo Clin Proc* 1995; 70: 725–33.
4. Fihn SD, *et al.* The risk for and severity of bleeding complications in elderly patients treated with warfarin. *Ann Intern Med* 1996; 124: 970–9.
5. Palareti G, *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348: 423–8.
6. Palareti G, *et al.* Oral anticoagulation treatment in the elderly: a nested, prospective, case-control study. *Arch Intern Med* 2000; 160: 470–8.
7. Fang MC, *et al.* Advanced age, anticoagulation intensity, and risk for intracranial hemorrhage among patients taking warfarin for atrial fibrillation. *Ann Intern Med* 2004; 141: 745–52.
8. Palareti G, Legnani C. Warfarin withdrawal: pharmacokinetic-pharmacodynamic considerations. *Clin Pharmacokinet* 1996; 30: 300–13.

Effects on the bones. Vitamin K is involved in bone metabolism and vitamin K deficiency is associated with an increased risk of osteoporotic fractures. It has been suggested, therefore, that patients on long-term treatment with those oral anticoagulants that are vitamin K antagonists may be at increased risk of osteoporosis and fractures. However, two large observational studies in older women have produced conflicting results. A prospective study[1] of both users and nonusers of warfarin found that warfarin was not associated with decrease in bone density or increase in fracture rates. A retrospective study[2] reported an association between long-term anticoagulant use and increased risk of vertebral and rib fractures, compared with the general population. Overall, however, the risk of any fracture was not significantly increased.

1. Jamal SA, *et al.* Warfarin use and risk for osteoporosis in elderly women. *Ann Intern Med* 1998; 128: 829–32.
2. Caraballo PJ, *et al.* Long-term use of oral anticoagulants and the risk of fracture. *Arch Intern Med* 1999; 159: 1750–6.

Effects on the fetus. Fetal complications of coumarin anticoagulants during pregnancy have been reviewed.[1–4]

1. Hall JG, *et al.* Maternal and fetal sequelae of anticoagulation during pregnancy. *Am J Med* 1980; 68: 122–40.
2. Chan WS, *et al.* Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. *Arch Intern Med* 2000; 160: 191–6.
3. Blickstein D, Blickstein I. The risk of fetal loss associated with warfarin anticoagulation. *Int J Gynaecol Obstet* 2002; 78: 221–5.
4. Bates SM, *et al.* VTE, thrombophilia, antithrombotic therapy, and pregnancy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e691S–736S.

Effects on the liver. There have been a few isolated reports of cholestatic liver damage in patients taking warfarin sodium,[1–3] which resolved on withdrawal.

1. Rehnqvist N. Intrahepatic jaundice due to warfarin therapy. *Acta Med Scand* 1978; 204: 335–6.
2. Jones DB, *et al.* Jaundice following warfarin therapy. *Postgrad Med J* 1980; 56: 671.
3. Adler E, *et al.* Cholestatic hepatic injury related to warfarin exposure. *Arch Intern Med* 1986; 146: 1837–9.

Effects on sexual function. There have been reports[1–5] of priapism in patients taking oral anticoagulants such as warfarin. As with warfarin-induced skin necrosis (see p. 1529.1), priapism appears to be associated with protein C deficiency, and the two conditions have frequently occurred together.

1. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; 4: 46–58.
2. Daryanani S, Wilde JT. Priapism in a patient with protein C deficiency. *Clin Lab Haematol* 1997; 19: 213–14.
3. Zimbelman J, *et al.* Unusual complications of warfarin therapy: skin necrosis and priapism. *J Pediatr* 2000; 137: 266–8.
4. Mahapatra M, *et al.* Priapism: an unusual manifestation of warfarin-induced skin necrosis with protein C deficiency. *J Assoc Physicians India* 2006; 54: 963–4.
5. Abu Sham'a RA, *et al.* Stuttering priapism complicating warfarin therapy in a patient with protein C deficiency. *Int J Lab Hematol* 2008; 30: 339–43.

Effects on the skin and hair. Skin and soft-tissue necrosis is a rare but well-established adverse effect of coumarin anticoagulants.[1-4] It is characterised by a localised, painful skin lesion, initially erythematous or haemorrhagic in appearance, that becomes bullous and eventually culminates in gangrenous necrosis. Fatalities have occurred. Areas of increased subcutaneous fat such as breast, thigh, and buttocks have most often been involved. The aetiology appears to be thrombotic but the exact pathophysiology is unknown. Patients with protein C deficiency appear to be at highest risk. Treatment with coumarin anticoagulants should be stopped if skin lesions appear and vitamin K should be given to reverse their effect. Heparin should be given to provide anticoagulation. Fresh frozen plasma or protein C concentrates may also have a role in reversing the condition. Surgical intervention is usually required if necrosis does develop.

Other skin reactions have also been reported with coumarins. Vasculitis affecting both legs developed in a 74-year-old woman a few weeks after starting treatment with acenocoumarol for deep-vein thrombosis and pulmonary embolism.[5] Acenocoumarol treatment was stopped and the skin lesions steadily improved over 15 days. However, the skin lesions reappeared a few hours after re-exposure to a single dose of acenocoumarol. The patient had also been taking amiodarone which may have contributed to the reaction. Henoch-Schönlein purpura was reported[6] in a 76-year-old woman 2 months after she started treatment with acenocoumarol; it resolved rapidly after the drug was withdrawn.

Increased shedding of telogen hair has been stated to occur in patients given coumarin anticoagulants.[7]

1. Cole MS, *et al.* Coumarin necrosis—a review of the literature. *Surgery* 1988; 103: 271–7.
2. Comp PC. Coumarin-induced skin necrosis: incidence, mechanisms, management and avoidance. *Drug Safety* 1993; 8: 128–35.
3. Chan YC, *et al.* Warfarin induced skin necrosis. *Br J Surg* 2000; 87: 266–72.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Warfarin-induced skin necrosis. *Aust Adverse Drug React Bull* 2005; 24: 23. Also available at: http://www.tga.gov.au/pdf/aadrb-0512.pdf (accessed 21/10/11)
5. Susano R, *et al.* Hypersensitivity vasculitis related to nicoumalone. *BMJ* 1993; 306: 973.
6. Borrás-Blasco J, *et al.* Acenocoumarol-induced Henoch-Schönlein purpura. *Ann Pharmacother* 2004; 38: 261–4.
7. Smith AG. Drug-induced disorders of hair and nails. *Adverse Drug React Bull* 1995 (173); 655–8.

Treatment of Adverse Effects

The methods used to manage bleeding and/or excessive anticoagulation during warfarin therapy, or after warfarin overdosage, depend upon the degree of bleeding, the value of the international normalised ratio (INR), and the degree of thromboembolic risk.

For patients **over-anticoagulated** on warfarin, the *British Society for Haematology* recommends the following:

- in non-bleeding patients with an INR over 5.0, withhold 1 or 2 doses of warfarin and reduce the maintenance dose
  - oral phytomenadione (vitamin K_1) may be considered if the INR is 5.0 to 8.0 and the patient is thought to be at high risk of bleeding
  - if the INR is over 8.0, give an oral dose of phytomenadione 1 to 5 mg
- in non-major bleeding, withhold or reduce the dose of warfarin and give intravenous phytomenadione 1 to 3 mg; tranexamic acid mouthwash may be useful for bleeding in the oral cavity
- in major bleeding, give a prothrombin complex concentrate infusion containing factors II, VII, IX, and X, at a dose of 25 to 50 units/kg, and intravenous phytomenadione 5 mg; fresh frozen plasma 15 to 30 mL/kg may be used if no concentrate is available but it will be less effective. Higher doses of phytomenadione have been used (see Over-anticoagulation, p. 2123.1); however phytomenadione takes several hours to act and large doses may reduce the response to resumed therapy with anticoagulants for a week or more.

US guidelines from the *American College of Chest Physicians* are as follows:

- if the INR is no more than 0.5 above the therapeutic range in a patient with previously stable therapeutic INRs, continue the current warfarin dose and test the INR within 1 to 2 weeks
- in non-bleeding patients, measures include withholding and adjusting the dose of warfarin; oral phytomenadione may be given when the INR is over 10.0
- in major bleeding, give a prothrombin complex concentrate and phytomenadione 5 to 10 mg by slow intravenous injection.

If bleeding occurs unexpectedly at therapeutic INR values, the possibility of an underlying cause such as renal or alimentary tract disease should be investigated.

See under Effects on the Skin and Hair, above, for the management of skin and soft tissue necrosis.

For poisoning in individuals not taking anticoagulant therapy, the *UK National Poisons Information Service* recommends that those who have ingested more than 250 micrograms/kg of warfarin or who have an INR greater than 4.0, should be given phytomenadione 10 to 20 mg orally. Infusion of prothrombin complex concentrate 30 to 50 units/kg should be given if there is active bleeding, and the dose of phytomenadione may be given by slow intravenous injection. Fresh frozen plasma 15 mL/kg may be used if concentrate is not available.

References.

1. Makris M, *et al.* Warfarin anticoagulation reversal: management of the asymptomatic and bleeding patient. *J Thromb Thrombolysis* 2010; 29: 171–81.
2. Goodnough LT, Shander A. How I treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage. *Blood* 2011; 117: 6091–9.
3. Keeling D, *et al.* British Committee for Standards in Haematology. Guidelines on oral anticoagulation with warfarin -fourth edition. *Br J Haematol* 2011; 154: 311–24. Correction. *ibid.*; 156: 150–2. Also available at: http://www.bcshguidelines.com/documents/warfarin_4th_ed.pdf (accessed 27/02/12)
4. Holbrook A, *et al.* Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 suppl): e152S–84S. Also available at: http://journal.publications.chestnet.org/data/Journals/CHEST/23443/112295.pdf (accessed 11/09/12)

Precautions

Warfarin should not be given to patients who are haemorrhaging. In general it should not be given to patients at serious risk of haemorrhage, although it has been used with very careful control; patients at risk include those with haemorrhagic blood disorders, peptic ulcer disease, severe wounds (including surgical wounds), cerebrovascular disorders, and bacterial endocarditis. Caution is also advised in patients with hepatic or renal impairment, and in those with uncontrolled hypertension. Consideration should be given to stopping warfarin a few days before an invasive procedure and using an alternative form of antithrombotic therapy. Pregnancy is generally considered to be a contra-indication, especially in the first trimester and during the late stages of pregnancy (see Adverse Effects, p. 1528.2). Warfarin should not be given to patients with heparin-induced thrombocytopenia until the platelet count has recovered.

Many factors may affect anticoagulant control with warfarin. These include vitamin K status, thyroid status, renal function, bioavailability differences between warfarin preparations, factors affecting absorption of warfarin, genetic variation in warfarin metabolism (see below), and drug interactions. Such factors may be responsible for apparent resistance to warfarin and a few patients have displayed hereditary resistance. Dosage alterations should be guided by regular monitoring of oral anticoagulant therapy and clinical status. Patients should carry anticoagulant treatment booklets.

A discussion of factors affecting the anticoagulant effect of warfarin sodium.[1]

1. Shetty HGM, *et al.* Clinical pharmacokinetic considerations in the control of oral anticoagulant therapy. *Clin Pharmacokinet* 1989; 16: 238–53.

Breast feeding. Drug concentrations were measured[1] in the plasma and milk of 13 women given 2 to 12 mg of warfarin daily. Plasma concentrations varied from 1.6 to 8.5 micromoles/litre but were below the limit of detection of 0.08 micromoles/litre in the breast milk or in the plasma of the 7 infants who were breast fed. No anticoagulant effect was found in the 3 breast-fed infants tested. In another report[2] of 2 women (dose of warfarin not specified), no evidence of the drug was found in the milk of one mother, and no anticoagulant effect was found in either infant. Last available guidance from the American Academy of Pediatrics considered[3] that warfarin is therefore usually compatible with breast feeding.

1. Orme MLE, *et al.* May mothers given warfarin breast-feed their infants? *BMJ* 1977; 1: 1564–5.
2. McKenna R, *et al.* Is warfarin sodium contraindicated in the lactating mother? *J Pediatr* 1983; 103: 325–7.
3. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 06/07/04)

Genetic variation. The response to warfarin and dosing requirements vary widely between individuals and between different racial groups.[1,2] Factors involved include age, indication for anticoagulation, diet, and use of interacting drugs, but much of the variability appears to be related to genetic polymorphism.[3] Two genes appear to be particularly important: the gene for the cytochrome P450 isoenzyme CYP2C9, the major enzyme involved in warfarin metabolism; and the gene for vitamin K epoxide reductase (VKOR), which is involved in the synthesis of clotting factors and is the major target for warfarin and other coumarin anticoagulants.[4,5] Although polymorphisms in either gene may affect dose requirements, patients with variant alleles for both genes appear to be particularly sensitive to warfarin;[6] initial variability in response may be more strongly associated with VKOR.[7] Identification of affected patients by genetic testing may be used to guide initial warfarin dosage, and dosage algorithms have been suggested, although they require validation.[8-13] Similar effects have also been noted with other coumarins, including acenocoumarol[14,15] and phenprocoumon.[15,16]

1. Dang M-TN, *et al.* The influence of ethnicity on warfarin dosage requirement. *Ann Pharmacother* 2005; 39: 1008–12.
2. Lam MPS, Cheung BMY. The pharmacogenetics of the response to warfarin in Chinese. *Br J Clin Pharmacol* 2012; 73: 340–7.
3. Kamali F, Wynne H. Pharmacogenetics of warfarin. *Annu Rev Med* 2010; 61: 63–75.
4. Schwarz UI, Stein CM. Genetic determinants of dose and clinical outcomes in patients receiving oral anticoagulants. *Clin Pharmacol Ther* 2006; 80: 7–12.
5. Takeuchi F, *et al.* A genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. *PLoS Genet* 2009; 5: e1000433.
6. Aquilante CL, *et al.* Influence of coagulation factor, vitamin K epoxide reductase complex subunit 1, and cytochrome P450 2C9 gene polymorphisms on warfarin dose requirements. *Clin Pharmacol Ther* 2006; 79: 291–302.
7. Schwarz UI, *et al.* Genetic determinants of response to warfarin during initial anticoagulation. *N Engl J Med* 2008; 358: 999–1008.
8. Stehle S, *et al.* Pharmacogenetics of oral anticoagulants: a basis for dose individualization. *Clin Pharmacokinet* 2008; 47: 565–94.
9. Wadelius M, *et al.* The largest prospective warfarin-treated cohort supports genetic forecasting. *Blood* 2009; 113: 784–92.
10. Klein TE, *et al.* International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. *N Engl J Med* 2009; 360: 753–64. Correction. *ibid.*; 361: 1613.
11. Lenzini P, *et al.* Integration of genetic, clinical, and INR data to refine warfarin dosing. *Clin Pharmacol Ther* 2010; 87: 572–8.
12. Johnson JA, *et al.* Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther* 2011; 90: 625–9.
13. Avery PJ, *et al.* EU-PACT Study Group. A proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clin Pharmacol Ther* 2011; 90: 701–6.
14. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation. *Clin Pharmacol Ther* 2006; 80: 13–22.
15. Cadamuro J, *et al.* Genetic determinants of acenocoumarol and phenprocoumon maintenance dose requirements. *Eur J Clin Pharmacol* 2010; 66: 253–60.
16. Schalekamp T, *et al.* VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. *Clin Pharmacol Ther* 2007; 81: 185–93.

Macular degeneration. Intra-ocular haemorrhage leading to loss of vision has been reported[1,2] in patients with neovascular (wet) age-related macular degeneration receiving warfarin, and caution has been advised[3] in such patients.

1. Tilanus MAD, *et al.* Relationship between anticoagulant medication and massive intraocular hemorrhage in age-related macular degeneration. *Graefes Arch Clin Exp Ophthalmol* 2000; 238: 482–5.
2. Ung T, *et al.* Long term warfarin associated with bilateral blindness in a patient with atrial fibrillation and macular degeneration. *Heart* 2003; 89: 985.
3. Kowal LM, Harper CA. Visual complications of warfarin. *Med J Aust* 2002; 176: 351.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies warfarin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 28/10/11)

Spinal anaesthesia. Spinal haematomas have occurred after spinal or epidural anaesthesia or analgesia in patients taking warfarin. The optimum perioperative management of warfarinised patients receiving central nerve blocks remains controversial, but US guidelines[1] make the following recommendations:

- warfarin should be stopped ideally 4 to 5 days before the procedure to normalise the INR before giving a central nerve block. Other medicines that increase the risk of bleeding should not be given concurrently
- if warfarin is restarted postoperatively, indwelling catheters are most safely removed while the INR is below 1.5
- if the INR is between 1.5 and 3, catheter removal should be done with caution
- if the INR is greater than 3, the warfarin dose should be withheld or reduced in patients with indwelling catheters. The safety of removing a catheter at this level of INR is uncertain

1. Horlocker TT, *et al.* Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; 35: 64–101.

Interactions

Many compounds interact with warfarin and its related oral anticoagulants. Details of their drug interactions are given below; if the anticoagulant is other than warfarin, then its identity is specified. The major interactions are summarised in Table 7, p. 1530.1. Interactions of a pharmacodynamic nature occurring with one anticoagulant may well apply to

another but this may not be the case with pharmacokinetic interactions. Many food and herbal preparations also have the potential to interact with oral anticoagulants; some are discussed below.

An interaction may be due to increased or decreased anticoagulant metabolism; with warfarin some interacting drugs such as cimetidine, co-trimoxazole, or phenylbutazone have a selective effect on its stereo-isomers. Altered absorption may sometimes play a part, as with colestyramine. Displacement of oral anticoagulants from plasma protein binding sites has been reported with many drugs, including some analgesics. Not all reports that have recorded an alteration in the pharmacokinetics of the anticoagulant have, however, shown a corresponding change in clinical response.

Interference with the coagulation process may be responsible for the increased risk of haemorrhage when aspirin, clofibrate, or thyroid hormones are used with anticoagulants. Many other compounds, such as asparaginase, some contrast media, epoprostenol, streptokinase, and urokinase also carry this risk; while interactions between these compounds and anticoagulants are not discussed further below, the possibility of an increased risk of haemorrhage should be considered when they are used together.

Table 7. Summary of major interactions of warfarin and its related oral anticoagulants.

Drugs generally recognised as diminishing the effects of oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

acetomenaphthone	dichloralphenazone
alcohol (chronic ingestion without liver impairment)	ethchlorvynol
aminoglutethimide	griseofulvin
barbiturates	nafcillin
bosentan	phytomenadione
carbamazepine	rifampicin
	St John's wort

Drugs recognised or generally reported as enhancing oral anticoagulants are included in the following list. Further information on the interactions with these drugs and others where the interaction is not so well recognised is provided in the referenced section below.

alcohol (acute ingestion or chronic ingestion with liver impairment)	ethylestrenol
allopurinol	fluconazole
amiodarone	glucagon
aspirin	itraconazole
cefamandole	ketoconazole
chloramphenicol	metronidazole
cimetidine	miconazole
clofibrate	norethandrolone
cloral hydrate	NSAIDs
co-trimoxazole	oxymetholone
danazol	quinidine
dextropropoxyphene	stanozolol
dipyridamole	sulfinpyrazone
disulfiram	tamoxifen
erythromycin	telithromycin
etacrynic acid	thyroid agents
	tramadol
	triclofos sodium

Where there is a risk of serious haemorrhage from an interaction, then use of both drugs is best avoided. In other instances the anticoagulant activity should be carefully monitored so as to increase or decrease the anticoagulant dose as required. Critical periods are when patients stabilised on an anticoagulant start treatment with an interacting drug, or when patients stabilised on a regimen of an interacting drug and anticoagulant have the interacting drug withdrawn. Depending on the mechanism of the interaction, the clinical response to the interaction may be rapid or may take some days. Interactions involving displacement from plasma protein binding sites are often transient. Some interacting drugs do not produce predictable effects; there have for instance been reports of increased as well as decreased anticoagulant activity with disopyramide, phenytoin, quinidine, and oral contraceptives. Another problem occurs with dipyridamole; it can cause bleeding when given to patients taking anticoagulants but without any alteration in prothrombin times.

Reviews.

1. Harder S, Thürmann P. Clinically important drug interactions with anticoagulants: an update. *Clin Pharmacokinet* 1996; 30: 416–44.
2. Greenblatt DJ, von Moltke LL. Interaction of warfarin with drugs, natural substances, and foods. *J Clin Pharmacol* 2005; 45: 127–32.

Alcohol. Alcohol has a variable effect on warfarin. Heavy regular drinkers may have a diminished effect, perhaps through enzyme induction, although the effect of warfarin may be increased in the presence of liver impairment; acute ingestion has enhanced the effect of warfarin. A moderate alcohol intake is generally not considered to cause problems.

Analgesics and NSAIDs. All NSAIDs should be used with caution or not at all in patients on warfarin. Many NSAIDs inhibit platelet function to some extent and have an irritant effect on the gastrointestinal tract, so increasing the risk of haemorrhage. Furthermore, some NSAIDs increase the hypoprothrombinaemic effect of warfarin, possibly by an intrinsic effect on coagulation or by displacement of warfarin from plasma protein-binding sites. Many studies have compared the relative displacing action of a range of NSAIDs *in vitro*, but such studies cannot easily be extrapolated to the clinical situation. Changes in plasma concentration of unbound warfarin resulting from displacement from plasma protein-binding sites are usually transient and are most likely to occur in the first few weeks after an NSAID is added to or withdrawn from warfarin therapy; monitoring of anticoagulant therapy is, therefore, most critical during this period.

High doses of *aspirin* and some other *salicylates* enhance the hypoprothrombinaemic effect of warfarin and should generally be avoided in patients on oral anticoagulant therapy. Low-dose aspirin with warfarin may have a role in some patients but the risk of gastrointestinal bleeding is increased. The possibility of an interaction with topical salicylates should also be considered.[1,2]

Use of *phenylbutazone* with warfarin has led to serious haemorrhage and should be avoided. Phenylbutazone affects the metabolism of the *R*- and *S*- isomers of warfarin in complex and different ways with the net effect of enhancing its anticoagulant activity.[3] Related drugs such as *oxyphenbutazone*, *azapropazone*,[4-6] and *feprazone*[7] behave similarly and should also be avoided.

For the following NSAIDs there are a few studies or isolated reports suggesting that they may enhance the hypoprothrombinaemic effect of warfarin or other specified oral anticoagulant: *diflunisal* (with acenocoumarol[8] or warfarin[9]), *flurbiprofen* (with acenocoumarol),[10] *indometacin*,[11,12] *ketoprofen*,[13] *meclofenamate sodium*,[14] *mefenamic acid*,[15] *piroxicam*, (with warfarin[16] or acenocoumarol[17]), *sulindac*,[18,19] *tiaprofenic acid* (with acenocoumarol),[20] and *tolmetin sodium*.[21] In many cases the result of concomitant therapy was an increased prothrombin time which may or may not be clinically significant; in other cases haemorrhage occurred. It should also be noted that for many of the above NSAIDs, perhaps particularly indometacin, there are studies (not cited) in which no enhancement of warfarin activity was found. NSAIDs with an apparently minimal effect on warfarin activity include *etodolac*, *ibuprofen*, and *naproxen*.

Interactions have also been reported with NSAIDs that are selective inhibitors of cyclo-oxygenase-2. As with other NSAIDs, some studies (not cited) have shown a lack of interaction between warfarin and *celecoxib*, but there have been several reports[22-25] of an increase in the INR with concomitant therapy and bleeding has occurred in some patients.[24] Increases in INR were also reported in studies[25,26] of warfarin with *rofecoxib*; and there were reports of bleeding.[27] A small increase in INR was also reported[28] with *etoricoxib* in healthy subjects but was thought unlikely to be of clinical significance in most patients.

In view of the above considerations, *paracetamol* is recommended as the general analgesic and antipyretic of choice in patients on oral anticoagulant therapy. However, caution is needed since, although it has no effect on the gastric mucosa or on platelet function, some studies (with warfarin, anisindione, dicoumarol, or phenprocoumon)[29-31] and isolated reports[32,33] have found an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant. An increase in INR has also been reported[34,35] in controlled studies of the use of paracetamol in patients stabilised on warfarin. Increased monitoring of anticoagulant therapy may be appropriate for those also taking paracetamol regularly.

Opioid analgesics do not generally cause problems. However, there have been reports of enhanced anticoagulant activity in patients given *tramadol* with warfarin[36,37] including 2 deaths from haemorrhagic stroke,[37] and also with phenprocoumon,[38] although a randomised, double-blind, placebo-controlled study[39] in 19 patients failed to find evidence of an interaction between phenprocoumon and tramadol. *Co-proxamol*, a combination of *dextropropoxyphene* and paracetamol, has increased the effect of warfarin.[40-42] *Co-codamol*, a combination of *codeine* and paracetamol, has also enhanced warfarin activity.[43]

Amongst other analgesics, *glafenine* has been reported to possibly enhance the activity of phenprocoumon.[44] *Phenazone*, an inducer of enzyme metabolism, reduces plasma concentrations of warfarin and, in contrast with most other analgesics, may necessitate an increase in warfarin dosage.[45]

1. Chow WH, *et al.* Potentiation of warfarin anticoagulation by topical methylsalicylate ointment. *J R Soc Med* 1989; 82: 501–2.
2. Littleton F. Warfarin and topical salicylates. *JAMA* 1990; 263: 2888.
3. Banfield C, *et al.* Phenylbutazone-warfarin interaction in man: further stereochemical and metabolic considerations. *Br J Clin Pharmacol* 1983; 16: 669–75.
4. Powell-Jackson PR. Interaction between azapropazone and warfarin. *BMJ* 1977; 1: 1193–4.
5. Green AE, *et al.* Potentiation of warfarin by azapropazone. *BMJ* 1977; 1: 1532.
6. Win N, Mitchell DC. Azapropazone and warfarin. *BMJ* 1991; 302: 969–70.
7. Chierichetti S, *et al.* Comparison of feprazone and phenylbutazone interaction with warfarin in man. *Curr Ther Res* 1975; 18: 568–72.
8. Tempero KF, *et al.* Diflunisal: a review of pharmacokinetic and pharmacodynamic properties, drug interactions, and special tolerability studies in humans. *Br J Clin Pharmacol* 1977; 4 (suppl 1): 31S–36S.
9. Serlin MJ, *et al.* The effect of diflunisal on the steady state pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1980; 9: 287P–8P.
10. Stricker BHC, Delhez JL. Interaction between flurbiprofen and coumarins. *BMJ* 1982; 285: 812–13.
11. Koch-Weser J. Hemorrhagic reactions and drug interactions in 500 warfarin-treated patients. *Clin Pharmacol Ther* 1973; 14: 139.
12. Self TH, *et al.* Drug enhancement of warfarin activity. *Lancet* 1975; ii: 557–8.
13. Flessner MF. Prolongation of prothrombin time and severe gastrointestinal bleeding associated with combined use of warfarin and ketoprofen. *JAMA* 1988; 259: 353.
14. Baragar FD, Smith TC. Drug interaction studies with sodium meclofenamate (Meclomen). *Curr Ther Res* 1978; 23 (suppl 4): 551–559
15. Holmes EL. Experimental observations on flufenamic, mefenamic, and meclofenamic acids; IV: Toleration by normal human subjects. *Ann Phy Med* 1966; 9 (suppl): 36–49.
16. Rhodes RS, *et al.* A warfarin-piroxicam drug interaction. *Drug Intell Clin Pharm* 1985; 19: 556–8.
17. Bonnabry P, *et al.* Stereoselective interaction between piroxicam and acenocoumarol. *Br J Clin Pharmacol* 1996; 41: 525–30.
18. Carter SA. Potential effect of sulindac on response of prothrombin-time to oral anticoagulants. *Lancet* 1979; ii: 698–9.
19. Ross JRY, Beeley L. Sulindac, prothrombin time, and anticoagulants. *Lancet* 1979; ii: 1075.
20. Whittaker SJ, *et al.* A severe, potentially fatal, interaction between tiaprofenic acid and nicoumalone. *Br J Clin Pract* 1986; 40: 440.
21. Koren JF, *et al.* Tolmetin-warfarin interaction. *Am J Med* 1987; 82: 1278–9.
22. Mersfelder TL, Stewart LR. Warfarin and celecoxib interaction. *Ann Pharmacother* 2000; 34: 325–7.
23. Haase KK, *et al.* Potential interaction between celecoxib and warfarin. *Ann Pharmacother* 2000; 34: 666–7.
24. Adverse Drug Reactions Advisory Committee (ADRAC). Interaction of celecoxib and warfarin. *Aust Adverse Drug React Bull* 2001; 20: 2. Also available at: http://www.tga.gov.au/pdf/aadrb-0102.pdf (accessed 21/10/11)
25. Schaefer MG, *et al.* Interaction of rofecoxib and celecoxib with warfarin. *Am J Health-Syst Pharm* 2003; 60: 1319–23.
26. Schwartz JI, *et al.* The effect of rofecoxib on the pharmacodynamics and pharmacokinetics of warfarin. *Clin Pharmacol Ther* 2000; 68: 626–36.
27. Adverse Drug Reactions Advisory Committee (ADRAC). Interaction of rofecoxib with warfarin. *Aust Adverse Drug React Bull* 2002; 21: 3. Also available at: http://www.tga.gov.au/pdf/aadrb-0202.pdf (accessed 21/10/11)
28. Schwartz JI, *et al.* The effect of etoricoxib on the pharmacodynamics and pharmacokinetics of warfarin. *J Clin Pharmacol* 2007; 47: 620–7.
29. Antlitz AM, *et al.* Potentiation of oral anticoagulant therapy by acetaminophen. *Curr Ther Res* 1968; 10: 501–7.
30. Hylek EM, *et al.* Acetaminophen and other risk factors for excessive warfarin anticoagulation. *JAMA* 1998; 279: 657–62.
31. Launiainen T, *et al.* Adverse interaction of warfarin and paracetamol: evidence from a post-mortem study. *Eur J Clin Pharmacol* 2010; 66: 97–103.
32. Boeijinga JJ, *et al.* Interaction between paracetamol and coumarin anticoagulants. *Lancet* 1982; i: 506.
33. Dharmarajan L, Sajjad W. Potentially lethal acetaminophen-warfarin interaction in an older adult: an under-recognized phenomenon? *J Am Med Dir Assoc* 2007; 8: 545–7.
34. Mahé I, *et al.* Paracetamol: a haemorrhagic risk factor in patients on warfarin. *Br J Clin Pharmacol* 2005; 59: 371–4.
35. Zhang Q, *et al.* Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. *Eur J Clin Pharmacol* 2011; 67: 309–14.
36. Scher ML, *et al.* Potential interaction between tramadol and warfarin. *Ann Pharmacother* 1997; 31: 646–7.
37. Adverse Drug Reactions Advisory Committee (ADRAC). Tramadol–warfarin interaction. *Aust Adverse Drug React Bull* 2004; 23: 16. Also available at: http://www.tga.gov.au/pdf//aadrb-0408.pdf (accessed 21/10/11)
38. Madsen H, *et al.* Interaction between tramadol and phenprocoumon. *Lancet* 1997; 350: 637.
39. Boeijinga JK, *et al.* Lack of interaction between tramadol and coumarins. *J Clin Pharmacol* 1998; 38: 966–70.
40. Orme M, *et al.* Warfarin and Distalgesic interaction. *BMJ* 1976; 1: 200
41. Jones RV. Warfarin and Distalgesic interaction. *BMJ* 1976; 1: 460.
42. Smith R, *et al.* Propoxyphene and warfarin interaction. *Drug Intell Clin Pharm* 1984; 18: 822.
43. Bartle WR, Blakely JA. Potentiation of warfarin anticoagulation by acetaminophen. *JAMA* 1991; 265: 1260.
44. Boeijinga JK, van der Vijgh WJF. Double blind study of the effect of glafenine (Glifanan) on oral anticoagulant therapy with phenprocoumon (Marcumar). *J Clin Pharmacol* 1977; 12: 291–6.
45. Whitfield JB, *et al.* Changes in plasma γ-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; 1: 316–18.

Antiarrhythmics. *Amiodarone* has been shown in several studies to increase the activity of warfarin[1-7] and aceno-

coumarol,[8,9] probably through inhibition of metabolism. The potentiating effect of amiodarone has been reported to persist for up to 4 months after its withdrawal.[1] Phenprocoumon has been reported to be either unaffected[10] or potentiated[11] by amiodarone. Isolated reports with *disopyramide*[12] and *quinidine*[13] have suggested that these drugs can enhance the anticoagulant effect of warfarin. In 7 patients on warfarin or dicoumarol treated with disopyramide or quinidine, however, all but one needed a small increase in the weekly anticoagulant dose suggesting that the antiarrhythmic had reduced the anticoagulant effect.[14] Since the effect was seen after conversion of atrial fibrillation to sinus rhythm an involvement of haemodynamic factors was postulated. Several studies (not cited) have failed to show an effect of quinidine on warfarin. There are also reports indicating that *dronedarone*,[15] *propafenone*,[16] and *moracizine*[17] can enhance warfarin.

1. Martinowitz U, *et al.* Interaction between warfarin sodium and amiodarone. *N Engl J Med* 1981; 304: 671–2.
2. Almog S, *et al.* Mechanism of warfarin potentiation by amiodarone: dose—and concentration—dependent inhibition of warfarin elimination. *Eur J Clin Pharmacol* 1985; 28: 257–61.
3. Watt AH, *et al.* Amiodarone reduces plasma warfarin clearance in man. *Br J Clin Pharmacol* 1985; 20: 707–9.
4. O'Reilly RA, *et al.* Interaction of amiodarone with racemic warfarin and its separated enantiomorphs in humans. *Clin Pharmacol Ther* 1987; 42: 290–4.
5. Kerin NZ, *et al.* The incidence, magnitude, and time course of the amiodarone-warfarin interaction. *Arch Intern Med* 1988; 148: 1779–81.
6. Lu Y, *et al.* Characteristics of the amiodarone–warfarin interaction during long-term follow-up. *Am J Health-Syst Pharm* 2008; 65: 947–52.
7. Edwin SB, *et al.* An evaluation of the early pharmacodynamic response after simultaneous initiation of warfarin and amiodarone. *J Clin Pharmacol* 2010; 50: 693–8.
8. Arboix M, *et al.* The potentiation of acenocoumarol anticoagulant effect by amiodarone. *Br J Clin Pharmacol* 1984; 18: 355–60.
9. Richard C, *et al.* Prospective study of the potentiation of acenocoumarol by amiodarone. *Eur J Clin Pharmacol* 1985; 28: 625–9.
10. Verstraete M, *et al.* Dissimilar effect of two anti-anginal drugs belonging to the benzofuran group on the action of coumarin derivatives. *Arch Int Pharmacodyn Ther* 1968; 176: 33–41.
11. Broekmans AW, Meyboom RHB. Potentiëring van het cumarine-effect door amiodaron (Cordarone). *Ned Tijdschr Geneeskd* 1982; 126: 1415–17.
12. Haworth E, Burroughs AK. Disopyramide and warfarin interaction. *BMJ* 1977; 2: 866–7.
13. Gazzaniga AB, Stewart DR. Possible quinidine-induced hemorrhage in a patient on warfarin sodium. *N Engl J Med* 1969; 280: 711–12.
14. Sylvén C, Anderson P. Evidence that disopyramide does not interact with warfarin. *BMJ* 1983; 286: 1181.
15. Pogge EK, Haber SL. Elevated international normalized ratio associated with use of dronedarone and warfarin. *Ann Pharmacother* 2011; 45: e46.
16. Kates RE, *et al.* Interaction between warfarin and propafenone in healthy volunteer subjects. *Clin Pharmacol Ther* 1987; 42: 305–11.
17. Serpa MD, *et al.* Moricizine—warfarin: a possible drug interaction. *Ann Pharmacother* 1992; 26: 127.

Antibacterials. Several antibacterials have been involved in interactions with warfarin. Only a few reports are of serious effects and it is unlikely that any of the drugs need to be contra-indicated with warfarin; careful control should suffice.

Most of the drugs enhance the effects of warfarin. Apart from possible effects on the metabolism or plasma-protein binding of warfarin, some antibacterials may interfere with platelet function or with the bacterial synthesis of vitamin K in the gastrointestinal tract and thus have an anticoagulant effect of their own. This is generally considered unlikely to be of clinical significance except, perhaps, in patients with an inadequate vitamin K intake. Fever itself may increase the catabolism of clotting factors and exaggerate a potential antibacterial-warfarin interaction.

There are many reports of an enhanced warfarin response with *co-trimoxazole* and a significant association with increased bleeding has been confirmed;[1] stereospecific inhibition of warfarin metabolism is probably responsible.[2] The interaction is generally attributed to the *sulfamethoxazole* moiety and there are isolated reports suggesting that the activity of warfarin (or other specified oral anticoagulant) may be enhanced by other sulfonamides including *sulfafurazole*,[3] *sulfamethizole*,[4] and *sulfaphenazole* (with phenindione).[5]

There are several reports of potentiation of the effects of warfarin by *erythromycin* or its salts; inhibition of warfarin metabolism probably occurs. Although no clinically-significant increase in prothrombin time was found in 8 non-infected patients, the potential for an interaction was recognised.[6] An enhanced response to warfarin has also been reported with *azithromycin*,[7,8] with *roxithromycin*,[9] which included reports of spontaneous bleeding, and with *telithromycin*,[10,11] including a case of mild haemoptysis.[10] *Clarithromycin* may potentiate the effect of acenocoumarol[12] and of warfarin,[13] although other factors may also have been involved in this case.

Cefamandole has been reported to enhance the hypoprothrombinaemic response to warfarin.[14,15] Interference with vitamin K synthesis in the gastrointestinal tract and/or liver has been implicated. Related cephalosporins with an *N*-methylthiotetrazole side-chain such as *cefmetazole*, *cefmenoxime*, *cefoperazone*, and *latamoxef* may be expected to behave similarly although there appear to be no reports of an interaction. *Cefazolin*, which has a similar side-chain, may also enhance the effect of warfarin to some extent.[15] An elevated INR in a patient taking warfarin occurred on 2 separate occasions after the use of *ceftriaxone*.[16]

There have been reports of increased activity of warfarin (or other specified oral anticoagulant) by quinolone antibacterials including *nalidixic acid* (with warfarin[17,18] or acenocoumarol[19]), *ciprofloxacin*,[20-22] *gatifloxacin*,[22,23] *levofloxacin*,[22,24] *moxifloxacin*,[22,25] *norfloxacin*,[22,26] and *ofloxacin*,[27,28] although for some of these there are also studies indicating no effect (not cited). *Enoxacin* has been reported to decrease the clearance of *R*-warfarin but not *S*-warfarin; no prolongation of prothrombin time occurred.[29]

There are isolated reports suggesting an enhanced effect of warfarin (or other specified oral anticoagulant) with *aminosalicylic acid*,[30] *benzylpenicillin*,[31] *chloramphenicol* (with dicoumarol),[32] *doxycycline*,[33] *isoniazid*,[34] and *neomycin*.[35] Prothrombin times might be prolonged by broad-spectrum antibacterials such as *ampicillin*. There has been a report[36] of an increased INR and haematuria in a patient taking warfarin with *amoxicillin* and clavulanic acid, however, a randomised study[37] in 12 patients found no interaction between warfarin and amoxicillin with clavulanic acid. Warnings in licensed product information of potentiation of warfarin by *aztreonam*, *trimethoprim*, and *tetracyclines* other than doxycycline appear to have only a theoretical basis. The effect of *metronidazole* is discussed under Antiprotozoals, p. 1532.3.

Rifampicin diminishes the effect of warfarin by induction of metabolising enzymes in the liver. There are several reports of a similar effect with *nafcillin*[38-40] and with *dicloxacillin sodium*.[41,42]

When used for the treatment of traveller's diarrhoea, *rifaximin* is not expected to interact with warfarin because of its poor systemic bioavailability. However, a case of reduced effect of warfarin has been attributed to rifaximin used for the treatment of small bowel bacterial overgrowth. It was suggested that increased intestinal permeability, with the longer course and higher dose of rifaximin, enabled sufficient absorption of the antibacterial to result in liver enzyme induction.[43]

1. Fischer HD, *et al.* Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. *Arch Intern Med* 2010; 170: 617–21.
2. O'Reilly RA. Stereoselective interaction of trimethoprim-sulfamethoxazole with the separated enantiomorphs of racemic warfarin in man. *N Engl J Med* 1980; 302 33–5.
3. Sioris LJ, *et al.* Potentiation of warfarin anticoagulation by sulfisoxazole. *Arch Intern Med* 1980; 140: 546–7.
4. Lumholtz B, *et al.* Sulfamethizole-induced inhibition of diphenylhydantoin, tolbutamide, and warfarin metabolism. *Clin Pharmacol Ther* 1975; 17: 731–4.
5. Varma DR, *et al.* Prothrombin response to phenindione during hypoalbuminaemia. *Br J Clin Pharmacol* 1975; 2: 467–8.
6. Weibert RT, *et al.* Effect of erythromycin in patients receiving long-term warfarin therapy. *Clin Pharm* 1989; 8: 210–14.
7. Lane G. Increased hypoprothrombinemic effect of warfarin possibly induced by azithromycin. *Ann Pharmacother* 1996; 30: 884–5.
8. Woldtvedt BR, *et al.* Possible increased anticoagulation effect of warfarin induced by azithromycin. *Ann Pharmacother* 1998; 32: 269–70.
9. Anonymous. Interaction of warfarin with macrolide antibiotics. *Aust Adverse Drug React Bull* 1995; 14: 11. Also available at: http://www.tga.gov.au/hp/aadrb-9508.htm (accessed 21/10/11)
10. Kollekas L, *et al.* Potential interaction between telithromycin and warfarin. *Ann Pharmacother* 2004; 38: 1424–7.
11. Health Canada. Telithromycin (Ketek) and warfarin: suspected interaction. *Can Adverse React News* 2005; 15 (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v15n1-eng.pdf (accessed 21/10/11)
12. Grau E, *et al.* Interaction between clarithromycin and oral anticoagulants. *Ann Pharmacother* 1996; 30: 1495–6.
13. Recker MW, Kier KL. Potential interaction between clarithromycin and warfarin. *Ann Pharmacother* 1997; 31: 996–8.
14. Angaran DM, *et al.* The influence of prophylactic antibiotics on the warfarin anticoagulation response in the postoperative prosthetic cardiac valve patient. *Ann Surg* 1984; 199: 107–11.
15. Angaran DM, *et al.* The comparative influence of prophylactic antibiotics on the prothrombin response to warfarin in the postoperative prosthetic cardiac valve patient: cefamandole, cefazoline, vancomycin. *Ann Surg* 1987; 206: 155–61.
16. Clark TR, Burns S. Elevated international normalized ratio values associated with concomitant use of warfarin and ceftriaxone. *Am J Health-Syst Pharm* 2011; 68: 1603–5.
17. Hollbrand BI. Interaction of nalidixic acid and warfarin. *BMJ* 1974; 2: 666.
18. Leor J, *et al.* Interaction between nalidixic acid and warfarin. *Ann Intern Med* 1987; 107: 601.
19. Potasman I, Bassan H. Nicoumalone and nalidixic acid interaction. *Ann Intern Med* 1980; 92: 571.
20. Mott FE, *et al.* Ciprofloxacin and warfarin. *Ann Intern Med* 1989; 111: 542–3.
21. Kamada AK. Possible interaction between ciprofloxacin and warfarin. *DICP Ann Pharmacother* 1990; 24: 27–8.
22. Health Canada. Fluoroquinolones and warfarin: suspected interaction. *Can Adverse React News* 2004; 14 (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n3-eng.pdf (accessed 21/10/11)
23. Chock AWY, Stading JA. Indeterminable international normalized ratio with concurrent use of warfarin and gatifloxacin. *Am J Health-Syst Pharm* 2006; 63: 1539–42.
24. Jones CB, Fugate SE. Levofloxacin and warfarin interaction. *Ann Pharmacother* 2002; 36: 1554–7.
25. Elbe DHT, Chang SW. Moxifloxacin-warfarin interaction: a series of five case reports. *Ann Pharmacother* 2005; 39: 361–4.
26. Linville T, Matanin D. Norfloxacin and warfarin. *Ann Intern Med* 1989; 110: 751–2.
27. Leor J, Materzki S. Ofloxacin and warfarin. *Ann Intern Med* 1988; 109: 761.
28. Baciewicz AM, *et al.* Interaction of ofloxacin and warfarin. *Ann Intern Med* 1993; 119: 1223.
29. Toon S, *et al.* Enoxacin-warfarin interaction: pharmacokinetic and stereochemical aspects. *Clin Pharmacol Ther* 1987; 42: 33–41.
30. Self TH. Interaction of warfarin and aminosalicylic acid. *JAMA* 1973; 223: 1285.
31. Brown MA, *et al.* Interaction of penicillin-G and warfarin? *Can J Hosp Pharm* 1979; 32: 18–19.
32. Christensen LK, Skovsted L. Inhibition of drug metabolism by chloramphenicol. *Lancet* 1969; ii: 1397–9.
33. Westfall LK, *et al.* Potentiation of warfarin by tetracycline. *Am J Hosp Pharm* 1980; 37: 1620 and 1625.
34. Rosenthal AR, *et al.* Interaction of isoniazid and warfarin. *JAMA* 1977; 238: 2177.
35. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; 77 (Aug.): 20–5.
36. Davydov L, *et al.* Warfarin and amoxicillin/clavulanate drug interaction. *Ann Pharmacother* 2003; 37: 367–70.
37. Zhang Q, *et al.* Amoxicillin/clavulanic acid–warfarin drug interaction: a randomized controlled trial. *Br J Clin Pharmacol* 2011; 71: 232–6.
38. Qureshi GD, *et al.* Warfarin resistance with nafcillin therapy. *Ann Intern Med* 1984; 100: 527–9.
39. Fraser GL, *et al.* Warfarin resistance associated with nafcillin therapy. *Am J Med* 1989; 87: 237–8.
40. Davis RL, *et al.* Warfarin-nafcillin interaction. *J Pediatr* 1991; 118: 300–3.
41. Krstenansky PM, *et al.* Effect of dicloxacillin sodium on the hypoprothrombinemic response to warfarin sodium. *Clin Pharm* 1987; 6: 804–6.
42. Mailloux A, *et al.* Potential interaction between warfarin and dicloxacillin. *Ann Pharmacother* 1996; 30: 1402–7.
43. Hoffman JT, *et al.* Probable interaction between warfarin and rifaximin in a patient treated for small intestine bacterial overgrowth. *Ann Pharmacother* 2011; 45: e25.

Antidepressants. *Amitriptyline* and *nortriptyline* have been reported to prolong the half-life of dicoumarol in healthy subjects.[1,2] The few reports investigating the effect of tricyclic antidepressants on warfarin have not been able to conclude that a significant interaction exists. *Mianserin* and phenprocoumon have been reported not to interact.[3]

The *BNF* considers that there is a possible risk of increased coumarin activity with *SSRIs*; increased warfarin activity has been reported in a few patients taking *fluoxetine*[4] and in a patient taking *fluvoxamine*.[5] The SNRI *duloxetine* has also been reported[6] to increase warfarin activity, although a study in healthy subjects was unable to confirm this effect.[7] There have also been reports of increased anticoagulant activity in patients taking acenocoumarol and *citalopram*,[8] fluvoxamine, or *venlafaxine*.[9]

An increase in the dose of warfarin has been required by patients also taking *trazodone*.[10,11]

See also St John's Wort, p. 1535.2.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; 283: 1484–8.
2. Pond SM, *et al.* Effects of tricyclic antidepressants on drug metabolism. *Clin Pharmacol Ther* 1975; 18: 191–9.
3. Kopera H, *et al.* Phenprocoumon requirement, whole blood coagulation time, bleeding time and plasma γ-GT in patients receiving mianserin. *Eur J Clin Pharmacol* 1978; 13: 351–6.
4. Woolfrey S, *et al.* Fluoxetine-warfarin interaction. *BMJ* 1993; 307: 241.
5. Limke KK, *et al.* Fluvoxamine interaction with warfarin. *Ann Pharmacother* 2002; 36: 1890–2.
6. Glueck CJ, *et al.* Interaction of duloxetine and warfarin causing severe elevation of international normalized ratio. *JAMA* 2006; 295: 1517–18.
7. Chappell J, *et al.* Effects of duloxetine on the pharmacodynamics and pharmacokinetics of warfarin at steady state in healthy subjects. *J Clin Pharmacol* 2009; 49: 1456–66.
8. Borrás-Blasco J, *et al.* Probable interaction between citalopram and acenocoumarol. *Ann Pharmacother* 2002; 36: 345.
9. Teichert M, *et al.* Selective serotonin re-uptake inhibiting antidepressants and the risk of overanticoagulation during acenocoumarol maintenance treatment. *Br J Clin Pharmacol* 2011; 72: 798–805.
10. Hardy J-L, Sirois A. Reduction of prothrombin and partial thromboplastin times with trazodone. *Can Med Assoc J* 1986; 135: 1372.
11. Small NL, Giamonna KA. Interaction between warfarin and trazodone. *Ann Pharmacother* 2000; 34: 734–6.

Antidiabetics. There have been a few early instances of *tolbutamide* enhancing the activity of dicoumarol.[1] However, this effect has not been seen in later studies involving dicoumarol,[1-3] warfarin,[2] and phenprocoumon,[4] although one study did find altered dicoumarol pharmacokinetics.[3] An absence of effect has been documented for phenprocoumon and *insulin*, *glibenclamide*, or *glibornuride*,[4] but there is a report of glibenclamide enhancing the effect of warfarin.[5]

There has been an isolated report of bleeding in a patient taking *phenformin* and warfarin.[6] *Metformin* has been reported to diminish phenprocoumon activity.[7]

A study in healthy subjects found no pharmacokinetic interaction between *exenatide* and single-dose warfarin, and an insignificant reduction in INR.[8] However, licensed product information for exenatide warns that there have been reported cases of an increase in INR with this combination, sometimes associated with bleeding.

Coumarin anticoagulants may increase the hypoglycaemic effect of *sulfonylureas* (see p. 503.3).

An enhanced response to warfarin has been reported in a patient receiving *troglitazone*.[9]

1. Chaplin H, Cassell M. Studies on the possible relationship of tolbutamide to dicumarol in anticoagulant therapy. *Am J Med Sci* 1958; 235: 706–16.
2. Poucher RL, Vecchio TJ. Absence of tolbutamide effect on anticoagulant therapy. *JAMA* 1966; 197: 1069–70.
3. Jähnchen E, *et al.* Pharmacokinetic analysis of the interaction between dicoumarol and tolbutamide in man. *Eur J Clin Pharmacol* 1976; 10: 349–56.
4. Heine P, *et al.* The influence of hypoglycaemic sulphonylureas on elimination and efficacy of phenprocoumon following a single oral dose in diabetic patients. *Eur J Clin Pharmacol* 1976; 10: 31–6.
5. Jassal SV. *BMJ* 1991; 303: 789.

6. Hamblin TJ. Interaction between warfarin and phenformin. *Lancet* 1971; ii: 1323.
7. Ohnhaus EE, *et al.* The influence of dimethylbiguanide on phenprocoumon elimination and its mode of action: a drug interaction study. *Klin Wochenschr* 1983; 61: 851–8.
8. Soon D, *et al.* Effect of exenatide on the pharmacokinetics and pharmacodynamics of warfarin in healthy Asian men. *J Clin Pharmacol* 2006; 46: 1179–87.
9. Plowman BK, Morreale AP. Possible troglitazone—warfarin interaction. *Am J Health-Syst Pharm* 1998; 55: 1071.

Antiepileptics. Barbiturates such as *phenobarbital* and *primidone* diminish the activity of warfarin and other coumarins through increased metabolism. *Carbamazepine* is reported to have a similar effect.[1,2] Reports of the effect of *phenytoin* on anticoagulants do not provide a clear picture. There are reports of phenytoin enhancing the effects of warfarin[3,4] and of acenocoumarol,[5] and a report of initial enhancement of warfarin followed by decreased anticoagulant action.[6] Phenytoin has been reported to diminish the effect of dicoumarol.[7] Addition of *felbamate* has been reported[8] to necessitate a reduction in warfarin dosage. In another patient there was a transient increase in response to warfarin when *valproic acid* was started.[9] Valproate also inhibits platelet function and caution is required with warfarin and other anticoagulants.

For the effect of oral anticoagulants on phenytoin, see p. 543.1.

1. Hansen JM, *et al.* Carbamazepine-induced acceleration of diphenylhydantoin and warfarin metabolism in man. *Clin Pharmacol Ther* 1971; 12: 539–43.
2. Ross JRY, Beeley L. Interaction between carbamazepine and warfarin. *BMJ* 1980; 280: 1415–16.
3. Nappi JM. Warfarin and phenytoin interaction. *Ann Intern Med* 1979; 90: 852.
4. Panegyres PK, Rischbieth RH. Fatal phenytoin warfarin interaction. *Postgrad Med J* 1991; 67: 98.
5. Jose L, *et al.* Acenocoumarol and phenytoin toxicity in the presence of CYP2C9 mutation. *J Assoc Physicians India* 2008; 56: 250–2.
6. Levine M, Sheppard I. Biphasic interaction of phenytoin with warfarin. *Clin Pharm* 1984; 3: 200–3.
7. Hansen JM, *et al.* Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta Med Scand* 1971; 189: 15–19.
8. Tisdel KA, *et al.* Warfarin—felbamate interaction: first report. *Ann Pharmacother* 1994; 28: 805.
9. Guthrie SK, *et al.* Hypothesized interaction between valproic acid and warfarin. *J Clin Psychopharmacol* 1995; 15: 138–9.

Antifungals. *Griseofulvin* has been reported to diminish the activity of warfarin.[1-3] There are several reports indicating that *miconazole*, given either systemically or topically as the oral gel, may enhance the activity of oral anticoagulants (warfarin, ethyl biscoumacetate, acenocoumarol, and phenindione).[4-11] Absorption of miconazole after intravaginal use may have enhanced the activity of acenocoumarol in 2 patients;[12] it enhanced the activity of warfarin[13] in another. Studies in healthy subjects given a single warfarin dose[14,15] support case reports[16-18] suggesting that *fluconazole* may increase the anticoagulant activity of warfarin. There are isolated reports of the potentiation of warfarin by *itraconazole*[19] and *ketoconazole*,[20] and of unspecified coumarins by topical *bifonazole* or *econazole*.[21] A case-control study[22] in a cohort of warfarin users over 65 years old showed an increased risk of bleeding associated with the use of azole antifungals.

There has been a case report of a reduction in the effect of warfarin by *terbinafine*,[23] although a study[24] in healthy subjects found no clinically significant interaction, and others[25] considered that no interaction usually occurs. A case of potentiation of warfarin by terbinafine has also been reported;[26] the authors speculate that concomitant cimetidine may have contributed to the interaction by increasing plasma-terbinafine concentrations.

1. Cullen SI, Catalano PM. Griseofulvin-warfarin antagonism. *JAMA* 1967; 199: 582–3.
2. Udall JA. Drug interference with warfarin therapy. *Clin Med* 1970; 77 (Aug.): 20–5.
3. Okino K, Weibert RT. Warfarin-griseofulvin interaction. *Drug Intell Clin Pharm* 1986; 20: 291–3.
4. Loupi E, *et al.* Interactions médicamenteuses et miconazole: a propos de 10 observations. *Therapie* 1982; 37: 437–41.
5. Watson PG, *et al.* Drug interaction with coumarin derivative anticoagulants. *BMJ* 1982; 285: 1045–6.
6. Colquhoun MC, *et al.* Interaction between warfarin and miconazole oral gel. *Lancet* 1987; i: 695–6.
7. Bailey GM, *et al.* Miconazole and warfarin interaction. *Pharm J* 1989; 242: 183.
8. Ariyaratnam S, *et al.* Potentiation of warfarin anticoagulant activity by miconazole oral gel. *BMJ* 1997; 314: 349.
9. Evans J, *et al.* Treating oral candidiasis: potentially fatal. *Br Dent J* 1997; 182: 452.
10. Pemberton MN, *et al.* Derangement of warfarin anticoagulation by miconazole oral gel. *Br Dent J* 1998; 184: 68–9.
11. Ortin M, *et al.* Miconazole oral gel enhances acenocoumarol anticoagulant activity: a report of three cases. *Ann Pharmacother* 1999; 33: 175–7.
12. Lansdorp D, *et al.* Potentiation of acenocoumarol during vaginal administration of miconazole. *Br J Clin Pharmacol* 1999; 47: 225–6.
13. Thirion DJG, Farquhar Zanetti LA. Potentiation of warfarin's hypoprothrombinemic effect with miconazole vaginal suppositories. *Pharmacotherapy* 2000; 20: 98–9.
14. Lazar JD, Wilner KD. Drug interactions with fluconazole. *Rev Infect Dis* 1990; 12 (suppl 3): S327–S333.
15. Black DJ, *et al.* Warfarin–fluconazole II: a metabolically based drug interaction: in vivo studies. *Drug Metab Dispos* 1996; 24: 422–8.
16. Seaton TL, *et al.* Possible potentiation of warfarin by fluconazole. *DICP Ann Pharmacother* 1990; 24: 1177–8.
17. Gericke KR. Possible interaction between warfarin and fluconazole. *Pharmacotherapy* 1993; 13: 508–9.
18. Baciewicz AM, *et al.* Fluconazole—warfarin interaction. *Ann Pharmacother* 1994; 28: 1111.
19. Yeh J, *et al.* Potentiation of action of warfarin by itraconazole. *BMJ* 1990; 301: 669.
20. Smith AG. Potentiation of oral anticoagulants by ketoconazole. *BMJ* 1984; 288: 188–9. Correction. *ibid.*: 608.
21. Alexandra J-F, *et al.* Overanticoagulation with coumarin and cutaneous azole therapy. *Ann Intern Med* 2008; 148: 633–5.
22. Baillargeon J, *et al.* Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. *Am J Med* 2012; 125: 183–9.
23. Warwick JA, Corrall RJ. Serious interaction between warfarin and oral terbinafine. *BMJ* 1998; 316: 440.
24. Guerret M, *et al.* Evaluation of effects of terbinafine on single oral dose pharmacokinetics and anticoagulant actions of warfarin in healthy volunteers. *Pharmacotherapy* 1997; 17: 767–73.
25. Stockley IH. Terbinafine and warfarin mystery. *Pharm J* 1998; 260: 408.
26. Gupta AK, Ross GS. Interaction between terbinafine and warfarin. *Dermatology* 1998; 196: 266–7.

Antigout drugs. The drugs in this group most commonly implicated in interactions with anticoagulants are allopurinol and sulfinpyrazone.

With *allopurinol* there are conflicting reports of no interaction or an enhanced anticoagulant effect with dicoumarol,[1] phenprocoumon,[2] or warfarin.[3,4]

Interactions with *sulfinpyrazone* have usually involved warfarin and, apart from a case of a mixed response,[5] have involved increased anticoagulant activity, sometimes with haemorrhage, so calling for careful control. It is still not clear how sulfinpyrazone exerts its effect, but studies point to a stereoselective effect on warfarin metabolism where the *S*-isomer's metabolic clearance is inhibited;[6] sulfinpyrazone also affects platelets. Sulfinpyrazone has also enhanced the anticoagulant activity of acenocoumarol.[7] A significant interaction with phenprocoumon appears unlikely.[8]

Probenecid has accelerated the elimination of a single dose of phenprocoumon without effect on the prothrombin time.[9]

A study[10] of *benzbromarone* concluded that it enhanced the effect of warfarin by inhibition of the cytochrome P450 isoenzyme CYP2C9, leading to a stereoselective inhibition of the metabolism of warfarin.

1. Vesell ES, *et al.* Impairment of drug metabolism in man by allopurinol and nortriptyline. *N Engl J Med* 1970; 283: 1484–8.
2. Jähnchen E, *et al.* Interaction of allopurinol with phenprocoumon in man. *Klin Wochenschr* 1977; 55: 759–61.
3. Rawlins MD, Smith SE. Influence of allopurinol on drug metabolism in man. *Br J Pharmacol* 1973; 48: 693–8.
4. Pond SM, *et al.* The effects of allopurinol and clofibrate on the elimination of coumarin anticoagulants in man. *Aust N Z J Med* 1975; 5: 324–8.
5. Nenci GG, *et al.* Biphasic sulphinpyrazone-warfarin interaction. *BMJ* 1981; 282: 1361–2.
6. Toon S, *et al.* The warfarin-sulfinpyrazone interaction: stereochemical considerations. *Clin Pharmacol Ther* 1986; 39: 15–24.
7. Michot F, *et al.* Über die Beeinflussung der gerinnungshemmenden Wirkung von Acenocoumarol durch Sulfinpyrazon. *Schweiz Med Wochenschr* 1981; 111: 255–60.
8. Heimark LD, *et al.* The effect of sulfinpyrazone on the disposition of pseudoracemic phenprocoumon in humans. *Clin Pharmacol Ther* 1987; 42: 312–19.
9. Mönig H, *et al.* The effects of frusemide and probenecid on the pharmacokinetics of phenprocoumon. *Eur J Clin Pharmacol* 1990; 39: 261–5.
10. Takahashi H, *et al.* Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. *Clin Pharmacol Ther* 1999; 66: 569–81.

Antihistamines. There has been a report[1] of a raised INR and severe epistaxis in a patient after the addition of *cetirizine* to long-term acenocoumarol.

1. Berod T, Mathiot L. Probable interaction between cetirizine and acenocoumarol. *Ann Pharmacother* 1997; 31: 122.

Antimalarials. The ingestion of large amounts of tonic water by 2 patients necessitated a reduction in warfarin dosage. The enhanced effect was attributed to the *quinine* content of the tonic water.[1] A woman stabilised on warfarin developed haematuria and a high prothrombin ratio after taking *proguanil* for malaria prophylaxis.[2]

For an interaction with *atovaquone*, see Antiprotozoals, below.

1. Clark DJ. Clinical curio: warfarin and tonic water. *BMJ* 1983; 286: 1258.
2. Armstrong G, *et al.* Warfarin potentiated by proguanil. *BMJ* 1991; 303: 789.

Antimuscarinics. Cases of *tolterodine* enhancing the effect of warfarin have been reported.[1,2] In one,[1] it was stated that the manufacturers of tolterodine were aware of 6 reports of a possible interaction with warfarin. However, a study[3] in 20 healthy subjects found that tolterodine did not have a clinically significant effect on warfarin activity.

1. Colucci VJ, Rivey MP. Tolterodine–warfarin drug interaction. *Ann Pharmacother* 1999; 33: 1173–6.
2. Taylor JR. Probable interaction between tolterodine and warfarin. *Pharmacotherapy* 2006; 26: 719–21.
3. Rahimy M, *et al.* Effect of tolterodine on the anticoagulant actions and pharmacokinetics of single-dose warfarin in healthy volunteers. *Arzneimittelforschung* 2002; 52: 890–5.

Antineoplastics. There have been several reports of interactions between warfarin and antineoplastics. No clear picture emerges from these reports which is not surprising considering that antineoplastics are often given in combination and that they can exert their own haematological effects. *Cyclophosphamide* for instance has been associated with an increase in warfarin's activity when given with *methotrexate* and *fluorouracil*,[1] but with a decrease when given with non-antineoplastic drugs.[2] Fluorouracil and its prodrug *capecitabine* have elevated the prothrombin time and INR of patients taking warfarin, causing bleeding in some.[3] Licensed product information for capecitabine states that altered coagulation parameters and bleeding have also occurred with phenprocoumon. An increase in the effect of warfarin has been reported when given with fluorouracil and levamisole (see Levamisole, p. 1534.2). There have been 2 cases reported[4] where *trastuzumab* enhanced the effect of warfarin. *Etoposide* with *vindesine*[5] or with *carboplatin*,[6] *cisplatin*,[7] *ifosfamide* with *mesna*,[8] and *tamoxifen*[9] have all produced an increased anticoagulant effect. *Aminoglutethimide* has led to decreased activity of warfarin or acenocoumarol,[10,11] probably due to increased coumarin metabolism. Licensed product information for the anti-androgen *flutamide* states that increases in prothrombin time have been reported after starting flutamide therapy in patients on long-term warfarin. *In vitro* data indicate a similar reaction is likely with *bicalutamide*. *Mercaptopurine*[12] and *mitotane*[13] have also decreased warfarin activity. Licensed product information for *vorinostat* states that prolongation of prothrombin time has been seen when the drug is given with coumarin derivatives. Isolated cases of elevated INR and bleeding events have been reported when *erlotinib*,[14] *gefitinib*,[15] and *sorafenib*[16] were used with warfarin.

1. Seifter EJ, *et al.* Possible interactions between warfarin and antineoplastic drugs. *Cancer Treat Rep* 1985; 69: 244–5.
2. Tashima CK. Cyclophosphamide effect on coumarin anticoagulation. *South Med J* 1979; 72: 633–4.
3. Saif MW. An adverse interaction between warfarin and fluoropyrimidines revisited. *Clin Colorectal Cancer* 2005; 5: 175–80.
4. Nissenblatt MJ, Karp GI. Bleeding risk with trastuzumab (Herceptin) treatment. *JAMA* 1999; 282: 2299–2300.
5. Ward K, Bitran JD. Warfarin, etoposide, and vindesine interactions. *Cancer Treat Rep* 1984; 68: 817–18.
6. Le AT, *et al.* Enhancement of warfarin response in a patient receiving etoposide and carboplatin chemotherapy. *Ann Pharmacother* 1997; 31: 1006–8.
7. Yano R, *et al.* Transient elevation of international normalized ratio during cisplatin-based chemotherapy in patients who are taking warfarin. *Ann Pharmacother* 2011; 45: e55.
8. Hall G, *et al.* Intravenous infusions of ifosfamide/mesna and perturbation of warfarin anticoagulant control. *Postgrad Med J* 1990; 66: 860–1.
9. Givens CB, *et al.* Safety of concomitant tamoxifen and warfarin. *Ann Pharmacother* 2009; 43: 1867–71.
10. Lønning PE, *et al.* The influence of a graded dose schedule of aminoglutethimide on the disposition of the optical enantiomers of warfarin in patients with breast cancer. *Cancer Chemother Pharmacol* 1986; 17: 177–81.
11. Bruning PF, Bonfrèr JGM. Aminoglutethimide and oral anticoagulant therapy. *Lancet* 1983; ii: 582.
12. Spiers ASD, Mibashan RS. Increased warfarin requirement during mercaptopurine therapy: a new drug interaction. *Lancet* 1974; ii: 221–2.
13. Cuddy PG, *et al.* Influence of mitotane on the hypoprothrombinemic effect of warfarin. *South Med J* 1986; 79: 387–8.
14. Thomas KS, *et al.* Elevated international normalized ratio associated with concomitant warfarin and erlotinib. *Am J Health-Syst Pharm* 2010; 67: 1426–9.
15. Onoda S, *et al.* Drug interaction between gefitinib and warfarin. *Jpn J Clin Oncol* 2005; 35: 478–82.
16. Moretti LV, Montalvo RO. Elevated international normalized ratio associated with concurrent use of sorafenib and warfarin. *Am J Health-Syst Pharm* 2009; 66: 2123–5.

Antiplatelets. The interaction between anticoagulants and *dipyridamole* is unusual as bleeding can occur without any alteration in prothrombin times; special care is therefore required. This interaction has involved a small number of patients taking dipyridamole and warfarin or phenindione;[1] inhibition of platelet function by dipyridamole has been implicated. However, in general it does not appear to increase the risk of bleeding.[2]

Paradoxically, addition of *ticlopidine* was found to significantly increase acenocoumarol requirements.[3]

See also under Analgesics and NSAIDs (p. 1530.2).

1. Kalowski S, Kincaid-Smith P. Interaction of dipyridamole with anticoagulants in the treatment of glomerulonephritis. *Med J Aust* 1973; 2: 164–6.
2. Levine MN, *et al.* Hemorrhagic complications of long-term anticoagulan therapy. *Chest* 1989; 95 (suppl): 26S–36S.
3. Salar A, *et al.* Ticlopidine antagonizes acenocoumarol treatment. *Thromb Haemost* 1997; 77: 223–4.

Antiprotozoals. *Metronidazole* enhances the activity of warfarin[1,2] through selective inhibition of the metabolism of its *S*-isomer.[3]

A raised INR has been reported[4] in a patient taking warfarin after *atovaquone* was added to therapy.

1. Kazmier FJ. A significant interaction between metronidazole and warfarin. *Mayo Clin Proc* 1976; 51: 782–4.
2. Dean RP, Talbert RL. Bleeding associated with concurrent warfarin and metronidazole therapy. *Drug Intell Clin Pharm* 1980; 14: 864–6.
3. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. *N Engl J Med* 1976; 295: 354–7.
4. Hidalgo K, *et al.* A potential interaction between warfarin and atovaquone. *Ann Pharmacother* 2011; 45: e3.

Antithyroid drugs. See Thyroid and Antithyroid Drugs, p. 1535.2.

Antivirals. Reductions in dosage of either warfarin[1] or acenocoumarol[2] were necessary in 2 patients receiving *interferon alfa* for hepatitis C. The interactions may have been due to decreased metabolism of the anticoagulant. A similar need for a reduced warfarin dose had also been noted in other patients taking *interferon alfa-2b* or *interferon beta*.[1] However, in a patient taking interferon alfa-2b with *ribavirin*,[3] the warfarin dose needed to be increased, probably due to the interaction between ribavirin and warfarin.

A literature review[4] found that among the antiretrovirals, those most likely to interact with warfarin were the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the HIV-protease inhibitors (HIV-PIs). Of the NNRTIs, there were 4 reported cases in which *nevirapine* reduced the effect of warfarin, and one in which *efavirenz* increased it. From reports involving HIV-PIs, *saquinavir* appeared to inhibit warfarin's metabolism, while *darunavir*, *nelfinavir*, *ritonavir*, and *ritonavir-boosted lopinavir* appeared to induce it. (Ritonavir has also been reported[5] to decrease the response to acenocoumarol.) One conflicting report was noted in which ritonavir inhibited warfarin's metabolism; inconsistent ritonavir adherence was suggested as a possible reason.

Up to October 2005 there had been 19 reports[6] received by the Canadian health authorities (Health Canada) of enhanced response to warfarin between 1 and 11 days after starting *oseltamivir*. The increased INR ranged from 3.2 to 10.9; however, there was not enough information to be certain of causality. In 3 other cases there was a decrease in INR on the addition of oseltamivir. A retrospective study[7] also showed increases in INR after the use of oseltamivir in 7 of 15 patients who had been previously stabilised on warfarin for at least 3 months; bleeding was recorded in 3 patients. However, a prospective study[8] of 20 subjects stabilised on warfarin but without a clinical indication for oseltamivir found that it had no effect on either the pharmacodynamics or pharmacokinetics of warfarin. It was suggested that the influenza virus might alter the response to warfarin,[8] but this has been questioned.[7]

1. Adachi Y, *et al.* Potentiation of warfarin by interferon. *BMJ* 1995; 311: 292.
2. Serrattice J, *et al.* Interferon-alpha 2b interaction with acenocoumarol. *Am J Hematol* 1998; 57: 89.
3. Schulman S. Inhibition of warfarin activity by ribavirin. *Ann Pharmacother* 2002; 36: 72–4.
4. Lieditke MD, Rathbun RC. Warfarin-antiretroviral interactions. *Ann Pharmacother* 2009; 43: 322–8.
5. Llibre JM, *et al.* Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002; 36: 621–3.
6. Health Canada. Oseltamivir (Tamiflu) and warfarin: suspected increase in INR. *Can Adverse React News* 2006; 16 (1): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v16n1-eng.pdf (accessed 19/08/08)
7. Lee S-H, *et al.* Effect of oseltamivir on bleeding risk associated with warfarin therapy: a retrospective review. *Clin Drug Investig* 2012; 32: 131–7.
8. Davies BE, *et al.* Effect of oseltamivir treatment on anticoagulation: a cross-over study in warfarinized patients. *Br J Clin Pharmacol* 2010; 70: 834–43.

Anxiolytic sedatives, hypnotics, and antipsychotics. *Barbiturates*, by inducing liver metabolism, can reduce the activity of anticoagulants. The *benzodiazepines* do not generally have any effect although there is the rare report of increased or decreased activity.

Although there is a report suggesting that *cloral hydrate* may decrease the effect of dicoumarol by enzyme induction,[1] other studies and experience indicate an increase in the anticoagulant activity of warfarin.[2–4] However, the increase is only transient and is probably the result of displacement of warfarin from plasma protein binding sites by the metabolite trichloroacetic acid.[2] *Triclofos sodium* appears to increase the activity of warfarin in a similar way.[5]

Reduced anticoagulant activity has been reported with *dichloralphenazone*,[6,7] *ethchlorvynol* (with dicoumarol),[8] and *haloperidol* (with phenindione).[9] Compounds such as *meprobamate* and *methaqualone* appear to have no effect.

1. Cucinell SA, *et al.* The effect of chloral hydrate on bishydroxycoumarin metabolism: a fatal outcome. *JAMA* 1966; 197: 366–8.
2. Sellers EM, Koch-Weser J. Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. *Ann N Y Acad Sci* 1971; 179: 213–25.
3. Boston Collaborative Drug Surveillance Program. Interaction between chloral hydrate and warfarin. *N Engl J Med* 1972; 286: 53–5.
4. Udall JA. Warfarin-chloral hydrate interaction: pharmacological activity and clinical significance. *Ann Intern Med* 1974; 81: 341–4.
5. Sellers EM, *et al.* Enhancement of warfarin-induced hypoprothrombinemia by triclofos. *Clin Pharmacol Ther* 1972; 13: 911–15.
6. Breckenridge A, Orme M. Clinical implications of enzyme induction. *Ann N Y Acad Sci* 1971; 179: 421–3.
7. Whitfield JB, *et al.* Changes in plasma α-glutamyl transpeptidase activity associated with alterations in drug metabolism in man. *BMJ* 1973; 1: 316–18.
8. Johansson S-A. Apparent resistance to oral anticoagulant therapy and influence of hypnotics on some coagulation factors. *Acta Med Scand* 1968; 184: 297–300.
9. Oakley DP, Lautch H. Haloperidol and anticoagulant treatment. *Lancet* 1963; ii: 1231.

Beta blockers. Beta blockers, particularly those with a high lipid solubility such as propranolol, may inhibit the metabolism of warfarin.[1] Although several studies have shown pharmacokinetic interactions between some beta blockers and oral anticoagulants, no effect on anticoagulant activity has generally been found. However, possible potentiation of the effect of warfarin by *propranolol*[2] has been reported.

1. Mantero F, *et al.* Effect of atenolol and metoprolol on the anticoagulant activity of acenocoumarin. *Br J Clin Pharmacol* 1984; 17: 94S–96S.
2. Bax NDS, *et al.* Inhibition of drug metabolism by β-adrenoceptor antagonists. *Drugs* 1983; 25 (suppl 2): 121–6.

Cannabis. Cannabis smoking was reported[1] to significantly increase the INR of a patient taking warfarin, resulting in bruising, epistaxis, and gastrointestinal bleeding.

1. Yamreudeewong W, *et al.* Probable interaction between warfarin and marijuana smoking. *Ann Pharmacother* 2009; 43: 1347–53.

Central stimulants. *Methylphenidate* has been reported both to increase the half-life of ethyl biscoumacetate,[1] and to have no effect on its half-life or anticoagulant activity.[2] *Prolintane* had no effect.[2]

1. Garrettson LK, *et al.* Methylphenidate interaction with both anticonvulsants and ethyl biscoumacetate: a new action of methylphenidate. *JAMA* 1969; 207: 2053.
2. Hague DE, *et al.* The effect of methylphenidate and prolintane on the metabolism of ethyl biscoumacetate. *Clin Pharmacol Ther* 1971; 12: 259–62.

Chamomile. A 70-year-old woman stabilised on warfarin developed multiple internal haemorrhages after she increased her use of chamomile lotion and consumption of chamomile tea to 4 or 5 times daily.[1] The interaction was considered to be due to the coumarin constituent of chamomile.

1. Segal R, Pilote L. Warfarin interaction with Matricaria chamomilla. *Can Med Assoc J* 2006; 174: 1281–2.

Chinese herbal remedies. There have been reports of increased anticoagulation in patients taking Chinese herbal remedies with warfarin.[1–7] The remedies have ranged from single ingredient herbal preparations to complex multi-ingredient products, sometimes sold under the same brand name but with very different compositions.

1. Yu CM, *et al.* Chinese herbs and warfarin potentiation by 'Danshen'. *J Intern Med* 1997; 241: 337–9.
2. Izzat MB, *et al.* A taste of Chinese medicine! *Ann Thorac Surg* 1998; 66: 941–2.
3. Page RL, Lawrence JD. Potentiation of warfarin by dong quai. *Pharmacotherapy* 1999; 19: 870–6.
4. Chan TYK. Interaction between warfarin and danshen (Salvia miltiorrhiza). *Ann Pharmacother* 2001; 35: 501–4.
5. Lam AY, *et al.* Possible interaction between warfarin and Lycium barbarum L. *Ann Pharmacother* 2001; 35: 1199–1201.
6. Wong ALN, Chan TYK. Interaction between warfarin and the herbal product Quilinggao. *Ann Pharmacother* 2003; 37: 836–8.
7. Su Q, Li Y. Interaction between warfarin and the herbal product Shengmai-yin: a case report of intracerebral hematoma. *Yonsei Med J* 2010; 51: 793–6.

Corticosteroids and corticotropin. Corticosteroids are associated with an increase in blood coagulability, but their extensive use with anticoagulants, and very few reports of interaction, suggests that any problems are rare. However, there are some reports of corticosteroids or corticotropin either enhancing[1–3] or diminishing[4] the effects of anticoagulants. A retrospective study[5] in patients on long-term warfarin therapy given short courses of oral corticosteroids found that in most cases (29 of 32) there was an increase in INR, suggesting that careful monitoring is required.

1. Van Gauwenberge H, Jaques LB. Haemorrhagic effect of ACTH with anticoagulants. *Can Med Assoc J* 1958; 79: 536–40.
2. Costedoat-Chalumeau N, *et al.* Potentiation of vitamin K antagonists by high-dose intravenous methylprednisolone. *Ann Intern Med* 2000; 132: 631–5.
3. Stading JA, *et al.* Effects of prednisone on the international normalized ratio. *Am J Health-Syst Pharm* 2006; 63: 2354–6. Correction. *ibid.* 2007; 64: 130.
4. Chatterjea JB, Salomon L. Antagonistic effect of ACTH and cortisone on the anticoagulant activity of ethyl biscoumacetate. *BMJ* 1954; 2: 790–2.
5. Hazlewood KA, *et al.* Effect of oral corticosteroids on chronic warfarin therapy. *Ann Pharmacother* 2006; 40: 2101–6.

Cough suppressants. An increase in the activity of warfarin has been reported in patients taking *noscapine*[1,2] or *oxolamine*.[3] A subsequent study[3] suggested that the dose of warfarin should be reduced by 50% if oxolamine was started.

See also Menthol, p. 1535.1.

1. Scordo MG, *et al.* Warfarin–noscapine interaction: a series of four case reports. *Ann Pharmacother* 2008; 42: 448–50.
2. Ohlsson S, *et al.* Noscapine may increase the effect of warfarin. *Br J Clin Pharmacol* 2008; 65: 277–8.
3. Min KA, *et al.* Effect of oxolamine on anticoagulant effect of warfarin. *Am J Health-Syst Pharm* 2006; 63: 153–6.

Cranberry. Between 1999 and 2003 the UK CSM[1] had received 5 reports suggesting an interaction between warfarin and cranberry juice. In 3 patients the activity of warfarin had been potentiated and one of them had died. In the other patients the INR was either reduced or unstable. By 2004 there had been 7 further reports of suspected interactions and the CSM advised[2] patients to avoid cranberry juice and other cranberry products while taking warfarin. However, despite case reports suggesting an increase in warfarin activity, the potential for a pharmacokinetic effect has been questioned,[3] and pharmacokinetic and pharmacodynamic studies[4–8] (some funded by producers of cranberry products) have failed to confirm an interaction.

1. CSM/MHRA. Possible interaction between warfarin and cranberry juice. *Current Problems* 2003; 29: 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
2. CSM/MHRA. Interaction between warfarin and cranberry juice: new advice. *Current Problems* 2004; 30: 10. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod=LatestReleased (accessed 23/06/06)
3. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. *Am J Health-Syst Pharm* 2007; 64: 490–4.
4. Li Z, *et al.* Cranberry does not affect prothrombin time in male subjects on warfarin. *J Am Diet Assoc* 2006; 106: 2057–61.
5. Lilja JJ, *et al.* Effects of daily ingestion of cranberry juice on the pharmacokinetics of warfarin, tizanidine, and midazolam—probes of CYP2C9, CYP1A2, and CYP3A4. *Clin Pharmacol Ther* 2007; 81: 833–9.
6. Ansell J, *et al.* The absence of an interaction between warfarin and cranberry juice: a randomized, double-blind trial. *J Clin Pharmacol* 2009; 49: 824–30.
7. Mellen CK, *et al.* Effect of high-dose cranberry juice on the pharmacodynamics of warfarin in patients. *Br J Clin Pharmacol* 2010; 70: 139–42.
8. Ngo N, *et al.* The warfarin-cranberry juice interaction revisited: A systematic in vitro-in vivo evaluation. *J Exp Pharmacol* 2010; 2010: 83–91.

Dermatological drugs. A patient's warfarin dose had to be increased when he started treatment with *etretinate*.[1]

1. Ostlere LS, *et al.* Reduced therapeutic effect of warfarin caused by etretinate. *Br J Dermatol* 1991; 124: 505–10.

Dietary supplements. There have been reports of an increased INR in patients taking warfarin and dietary supplements containing *glucosamine* with or without *chondroitin*,[1–3] and the UK CHM advises[4] that patients on warfarin should not take glucosamine. A similar effect has been reported[5] with *poliglusam*.

1. Rozenfeld V, *et al.* Possible augmentation of warfarin effect by glucosamine-chondroitin. *Am J Health-Syst Pharm* 2004; 61: 306–7.
2. Knudsen JF, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: case report and review of the literature and MedWatch database. *Pharmacotherapy* 2008; 28: 540–8.
3. Adverse Drug Reactions Advisory Committee (ADRAC). Interaction between glucosamine and warfarin. *Aust Adverse Drug React Bull* 2008; 27: 3. Also available at: http://www.tga.gov.au/pdf/aadrb-0802.pdf (accessed 21/10/11)
4. CHM/MHRA. Glucosamine adverse reactions and interactions. *Current Problems* 2006; 31: 8. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 31/07/08)
5. Huang S-S, *et al.* Chitosan potentiation of warfarin effect. *Ann Pharmacother* 2007; 41: 1912–14.

Disulfiram. Two reports suggesting that disulfiram enhances the activity of warfarin[1,2] were confirmed by a study in 8 healthy subjects.[3] Although inhibition of liver enzymes by disulfiram was considered responsible,[3] a later study[4] suggested that disulfiram acts directly on the liver to increase hypoprothrombinaemia. This interaction is complicated by the variable effects of alcohol on warfarin (see p. 1530.2). Special care is therefore called for when these drugs are used together.

1. Rothstein E. Warfarin effect enhanced by disulfiram. *JAMA* 1968; 206: 1574–5.
2. Rothstein E. Warfarin effect enhanced by disulfiram (Antabuse). *JAMA* 1972; 221: 1052–3.
3. O'Reilly RA. Interaction of sodium warfarin and disulfiram (Antabuse) in man. *Ann Intern Med* 1973; 78: 73–6.
4. O'Reilly RA. Dynamic interaction between disulfiram and separated enantiomorphs of racemic warfarin. *Clin Pharmacol Ther* 1981; 29: 332–6.

Diuretics. *Etacrynic acid* has been reported to enhance the activity of warfarin.[1] *Chlortalidone*[2] and *spironolactone*[3] have both been associated with a reduction in warfarin's activity in healthy subjects and it has been suggested that this might be a consequence of the diuresis concentrating the circulating clotting factors. A case of an interaction between warfarin and *potassium canrenoate*, leading to a marked INR increase (10.8) and bruising, has been reported.[4] It was suggested that warfarin bioavailability was increased because potassium canrenoate can displace warfarin from serum albumin and because both drugs undergo hepatic metabolism via CYP3A. However, it is not uncommon to use these two drugs together and it was suggested that this patient was more susceptible to a clinically significant interaction because she was homozygous for the warfarin-sensitive genotype VKORC1-1639AA.

Torasemide has been reported to enhance the activity of warfarin,[5] possibly by competing for metabolism through the cytochrome P450 isoenzyme CYP2C9 and by displacement of warfarin from protein-binding sites. However, *bumetanide*, *furosemide*, and the *thiazides* appear to have no effect on warfarin.

1. Petrick RJ, *et al.* Interaction between warfarin and ethacrynic acid. *JAMA* 1975; 231: 843–4.

2. O'Reilly RA, *et al.* Impact of aspirin and chlorthalidone on the pharmacodynamics of oral anticoagulant drugs in man. *Ann N Y Acad Sci* 1971; 179: 173–86.
3. O'Reilly RA. Spironolactone and warfarin interaction. *Clin Pharmacol Ther* 1980; 27: 198–201.
4. Maggini V, *et al.* A severe case of warfarin–canrenoate interaction: a role for genetic predisposition? *Br J Haematol* 2010; 150: 482–3.
5. Bird J, Carmona C. Probable interaction between warfarin and torsemide. *Ann Pharmacother* 2008; 42: 1893–8.

Endothelin receptor antagonists. A study in healthy subjects[1] showed that *bosentan* decreased the anticoagulant effect of warfarin; individual cases have also been reported.[2,3]

1. Weber C, *et al.* Effect of the endothelin-receptor antagonist bosentan on the pharmacokinetics and pharmacodynamics of warfarin. *J Clin Pharmacol* 1999; 39: 847–54.
2. Murphey LM, Hood EH. Bosentan and warfarin interaction. *Ann Pharmacother* 2003; 37: 1028–31.
3. Spangler ML, Saxena S. Warfarin and bosentan interaction in a patient with pulmonary hypertension secondary to bilateral pulmonary emboli. *Clin Ther* 2010; 32: 53–6.

Gastrointestinal drugs. Antacids may or may not interact with warfarin. *Bismuth carbonate* and *magnesium trisilicate* for example have been reported to reduce warfarin's absorption,[1] but *aluminium hydroxide* has been found to have no effect on warfarin or dicoumarol.[2] *Magnesium hydroxide*[2] has also been reported to have no effect on warfarin, but has increased the plasma concentrations of dicoumarol.[2]

There have been occasional reports of *sucralfate* diminishing the effect of warfarin.[3–5]

Histamine H_2-antagonists have been widely studied. There are several reports indicating that *cimetidine* can enhance the anticoagulant effect of warfarin and haemorrhage has occurred. Several studies show that cimetidine can increase the plasma concentration and half-life of warfarin and that there is a selective inhibitory effect on the metabolism of its *R*-isomer.[6–9] Not all these studies have, however, found an increase in prothrombin time. The effect of cimetidine on warfarin appears to be dose-dependent[6] and to be subject to interindividual variation;[8,9] careful monitoring is needed. Limited evidence suggests that cimetidine has a similar effect on the metabolism of acenocoumarol[10,11] and phenindione[10] but not of phenprocoumon.[12] Studies with *ranitidine* have generally been unable to show an effect on the metabolism of warfarin,[9,13] although in one study warfarin clearance was reduced.[6] There is a case report suggesting that potentiation of warfarin by ranitidine may occasionally occur.[14]

One study has suggested that the **proton pump inhibitor** *omeprazole* could inhibit the metabolism of *R*-warfarin although a clinically significant effect was unlikely.[15] While no evidence of an interaction was found in a retrospective study[16] of patients on acenocoumarol and omeprazole, an observational study suggested a risk of overanticoagulation when acenocoumarol is combined with *esomeprazole* or *lansoprazole*.[17] However, *pantoprazole* appears to have no effect on the pharmacokinetics or pharmacodynamics of warfarin[18] or phenprocoumon.[19]

The bulk **laxative** *psyllium* has been reported[20] to have no effect on warfarin, but in a retrospective cohort study, the use of *lactulose* in patients taking acenocoumarol or phenprocoumon was associated with raised INRs.[21]

Among **other** *gastrointestinal drugs*, a marked increase in the effect of warfarin has been reported in a patient when *cisapride* was added.[22]

A study[23] in healthy subjects found that *aprepitant* caused a small decrease in plasma concentration of the more active *S*-isomer of warfarin and there was also a decrease in INR.

A reduction in the response to warfarin with development of venous thrombosis has been reported in a patient receiving *mesalazine*,[24] and in another patient receiving *sulfasalazine*.[25]

1. McElnay JC, *et al.* Interaction of warfarin with antacid constituents. *BMJ* 1978; 2: 1166.
2. Ambre JJ, Fischer LJ. Effect of coadministration of aluminum and magnesium hydroxides on absorption of anticoagulants in man. *Clin Pharmacol Ther* 1973; 14: 231–7.
3. Mungall D, *et al.* Sucralfate and warfarin. *Ann Intern Med* 1983; 98: 557.
4. Rey AM, Gums JG. Altered absorption of digoxin, sustained-release quinidine, and warfarin with sucralfate administration. *DICP Ann Pharmacother* 1991; 25: 745–6.
5. Parrish RH, *et al.* Sucralfate-warfarin interaction. *Ann Pharmacother* 1992; 26: 1015–16.
6. Desmond PV, *et al.* Decreased oral warfarin clearance after ranitidine and cimetidine. *Clin Pharmacol Ther* 1984; 35: 338–41.
7. Choonara IA, *et al.* Stereoselective interaction between the R enantiomer of warfarin and cimetidine. *Br J Clin Pharmacol* 1986; 21: 271–7.
8. Sax MJ, *et al.* Effect of two cimetidine regimens on prothrombin time and warfarin pharmacokinetics during long-term warfarin therapy. *Clin Pharm* 1987; 6: 492–5.
9. Toon S, *et al.* Comparative effects of ranitidine and cimetidine on the pharmacokinetics and pharmacodynamics of warfarin in man. *Eur J Clin Pharmacol* 1987; 32: 165–72.
10. Serlin MJ, *et al.* Cimetidine: interaction with oral anticoagulants in man. *Lancet* 1979; ii: 317–19.
11. Gill TS, *et al.* Cimetidine-nicoumalone interaction in man: stereochemical considerations. *Br J Clin Pharmacol* 1989; 27: 469–74.
12. Harenberg J, *et al.* Cimetidine does not increase the anticoagulant effect of phenprocoumon. *Br J Clin Pharmacol* 1982; 14: 292–3.
13. Serlin MJ, *et al.* Lack of effect of ranitidine on warfarin action. *Br J Clin Pharmacol* 1981; 12: 791–4.
14. Baciewicz AM, Morgan PJ. Ranitidine-warfarin interaction. *Ann Intern Med* 1990; 112: 76–7.
15. Sutfin T, *et al.* Stereoselective interaction of omeprazole with warfarin in healthy men. *Ther Drug Monit* 1989; 11: 176–84.
16. Vreeburg EM, *et al.* Lack of effect of omeprazole on oral acenocoumarol anticoagulant therapy. *Scand J Gastroenterol* 1997; 32: 991–4.
17. Teichert M, *et al.* Proton pump inhibitors and the risk of overanticoagulation during acenocoumarol maintenance treatment. *Br J Haematol* 2011; 153: 379–85.
18. Duursema L, *et al.* Lack of effect of pantoprazole on the pharmacodynamics and pharmacokinetics of warfarin. *Br J Clin Pharmacol* 1995; 39: 700–3.
19. Ehrlich A, *et al.* Lack of pharmacodynamic and pharmacokinetic interaction between pantoprazole and phenprocoumon in man. *Eur J Clin Pharmacol* 1996; 51: 277–81.
20. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; 12: 491–5.
21. Visser LE, *et al.* Overanticoagulation associated with combined use of lactulose and acenocoumarol or phenprocoumon. *Br J Clin Pharmacol* 2004; 57: 522–4.
22. Darlington MR. Hypoprothrombinemia induced by warfarin sodium and cisapride. *Am J Health-Syst Pharm* 1997; 54: 320–1.
23. Depré M, *et al.* Effect of aprepitant on the pharmacokinetics and pharmacodynamics of warfarin. *Eur J Clin Pharmacol* 2005; 61: 341–6.
24. Martinella MA. Mesalamine and warfarin therapy resulting in decreased warfarin effect. *Ann Pharmacother* 1998; 32: 841–2.
25. Teefy AM, *et al.* Warfarin resistance due to sulfasalazine. *Ann Pharmacother* 2000; 34: 1265–8.

Ginkgo biloba. There is a report[1] of a woman stabilised on warfarin for 5 years who suffered an intracerebral haemorrhage 2 months after starting *Ginkgo biloba*, possibly due to the additive effect of the latter's antiplatelet activity. However, a study[2] in healthy subjects found no evidence that ginkgo affected warfarin pharmacokinetics or coagulation.

1. Matthews MK. Association of Ginkgo biloba with intracerebral hemorrhage. *Neurology* 1998; 50: 1933–4.
2. Jiang X, *et al.* Effect of ginkgo and ginger on the pharmacokinetics and pharmacodynamics of warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; 59: 425–32.

Ginseng. A reduction in the response to warfarin was reported[1] in a patient after taking a ginseng preparation. A study[2] in healthy subjects also found a small reduction in response, although another study[3] in 31 patients found no significant effect.

1. Janetzky K, Morreale AP. Probable interaction between warfarin and ginseng. *Am J Health-Syst Pharm* 1997; 54: 692–3.
2. Yuan C-S, *et al.* American ginseng reduces warfarin's effect in healthy patients: a randomized, controlled trial. *Ann Intern Med* 2004; 141: 23–7.
3. Lee YH, *et al.* Interaction between warfarin and Korean red ginseng in patients with cardiac valve replacement. *Int J Cardiol* 2010; 145: 275–6.

Glucagon. A dose-dependent enhancement of warfarin's anticoagulant activity has been reported with glucagon.[1]

1. Koch-Weser J. Potentiation by glucagon of the hypoprothrombinemic action of warfarin. *Ann Intern Med* 1970; 72: 331–5.

Glucosamine. See Dietary Supplements, p. 1533.3.

Immunosuppressants. Severe bleeding occurred in a patient on long-term warfarin after stopping *azathioprine*,[1] while others[2,3] have needed an increased dose of warfarin when given with azathioprine.

There have been a few case reports of interaction between warfarin or acenocoumarol and *ciclosporin*, in which the dose of the anticoagulant or ciclosporin or both needed to be altered (see Anticoagulants under Interactions of Ciclosporin, p. 1957.3).

There has been a report[4] of *leflunomide* enhancing the effects of warfarin, causing gross haematuria after the second loading dose; the patient's INR rose from 3.4 to 11. It was stated that the UK CSM had received 4 reports of increased INR with leflunomide up to the end of 2002. In contrast, *teriflunomide* has been reported to decrease INR by 25% when given with warfarin.

1. Singleton JD, Conyers L. Warfarin and azathioprine: an important drug interaction. *Am J Med* 1992; 92: 217.
2. Rotenberg M, *et al.* Effect of azathioprine on the anticoagulant activity of warfarin. *Ann Pharmacother* 2000; 34: 120–2.
3. Vazquez SR, *et al.* Azathioprine-induced warfarin resistance. *Ann Pharmacother* 2008; 42: 1118–23.
4. Lim V, Pande I. Leflunomide can potentiate the anticoagulant effect of warfarin. *BMJ* 2002; 325: 1333. Correction. *ibid.* 2003; 326: 432.

Leukotriene antagonists. *Zafirlukast* is reported to decrease the clearance of *S*-warfarin.[1] Licensed product information for zafirlukast states that it probably inhibits the cytochrome P450 isoenzyme CYP2C9 which is involved in the metabolism of warfarin. Prothrombin time may be significantly prolonged when zafirlukast is added and warfarin dosage should be adjusted accordingly.

A study[2] of *montelukast* and warfarin found no significant interaction between the two drugs.

1. Suttle AB, *et al.* Effect of zafirlukast on the pharmacokinetics of R- and S-warfarin in healthy men. *Clin Pharmacol Ther* 1997; 61: 186.
2. Van Hecken, *et al.* Effect of montelukast on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers. *J Clin Pharmacol* 1999; 39: 495–500.

Levamisole. An increased INR has been reported[1] in a patient taking chronic warfarin therapy after addition of *levamisole* and fluorouracil, possibly due to inhibition of warfarin metabolism. Interactions between warfarin and other fluorouracil-containing regimens have been reported (see Antineoplastics, p. 1532.2) but levamisole might also be involved. In a second patient, a similar reaction was reported[2] after levamisole and fluorouracil and an episode of bleeding subsequently occurred after levamisole alone.

1. Scarfe MA, Israel MK. Possible drug interaction between warfarin and combination of levamisole and fluorouracil. *Ann Pharmacother* 1994; 28: 464–7.
2. Wehbe TW, Warth JA. A case of bleeding requiring hospitalization that was likely caused by an interaction between warfarin and levamisole. *Clin Pharmacol Ther* 1996; 59: 360–2.

Lipid regulating drugs. Fibrates have been reported to interact with coumarin anticoagulants, sometimes to the point of haemorrhage. *Bezafibrate* has been reported to enhance the effect of phenprocoumon[1] and warfarin,[2] and *fenofibrate*[3] and *gemfibrozil*[4,5] have been reported to enhance the effect of warfarin, although a study[6] in healthy subjects found that gemfibrozil slightly decreased plasma-warfarin concentrations. The mechanism of any interaction between coumarins and fibrates is not clear; a combination of pharmacokinetic and pharmacodynamic factors has been suggested.[5]

Interactions may also occur between statins and coumarin anticoagulants, and small studies and case reports have described increased warfarin activity, and sometimes bleeding, with *fluvastatin*,[7-9] *lovastatin*,[10] *rosuvastatin*[11,12] (also with acenocoumarol[13]), and *simvastatin*[14,15] (also with acenocoumarol[16]), although there are also reports in which no effect was seen.[17-19] Licensed product information for *pravastatin* states that no change in warfarin activity has been seen in patients given both drugs, although there has been a report[20] of bleeding in a patient taking fluindione when pravastatin was added. An epidemiological study[21] in patients stabilised on warfarin found that risk of hospitalisation from gastrointestinal bleeding was raised when *atorvastatin*, fluvastatin, or simvastatin, but not pravastatin, was added to therapy. A suggested mechanism was inhibition of warfarin metabolism via the cytochrome P450 isoenzyme CYP3A4, with pravastatin being noted as the only statin among these not significantly metabolised by cytochrome P450 isoenzymes. In the case of simvastatin, inhibition of both CYP2C9 and CYP3A4 has elsewhere been suggested[22] as a mechanism. A study[23] of health subjects showed no interaction between *pitavastatin* and warfarin.

Dextrothyroxine increases the anticoagulant effect of warfarin sodium[24,25] and dicoumarol.[26]

Colestyramine has reduced warfarin's serum concentration[27] and half-life[28] as well as its activity.[27,28] The mechanisms of this interaction include binding of warfarin to colestyramine and reduced absorption;[27] the enterohepatic recycling of warfarin may also be interrupted.[28] Phenprocoumon's activity has also been reduced by colestyramine.[29] However, colestyramine can also reduce vitamin K absorption, and this may result in hypoprothrombinaemia and bleeding.

Use of *omega-3 fatty acids* (as fish oil preparations) in patients taking warfarin and other antithrombotics has been associated with INR elevation[30] and subdural haematoma.[31] However, controlled studies in patients taking fish oil and warfarin[32,33] have failed to show an effect on bleeding episodes or bleeding time.

Benfluorex[34] and *colestipol*[35] have been reported not to interact with phenprocoumon.

1. Zimmermann R, *et al.* The effect of bezafibrate on the fibrinolytic enzyme system and the drug interaction with racemic phenprocoumon. *Atherosclerosis* 1978; 29: 477–85.
2. Beringer TRO. Warfarin potentiation with bezafibrate. *Postgrad Med J* 1997; 73: 657–8.
3. Ascah KJ, *et al.* Interaction between fenofibrate and warfarin. *Ann Pharmacother* 1998; 32: 765–8.
4. Ahmad S. Gemfibrozil interaction with warfarin sodium (Coumadin). *Chest* 1990; 98: 1041–2.
5. Dixon DL, Williams VG. Interaction between gemfibrozil and warfarin: case report and review of the literature. *Pharmacotherapy* 2009; 29: 744–8.
6. Lilja JJ, *et al.* Effect of gemfibrozil on the pharmacokinetics and pharmacodynamics of racemic warfarin in healthy subjects. *Br J Clin Pharmacol* 2005; 59: 433–9.
7. Andrus MR. Oral anticoagulant drug interactions with statins: case report of fluvastatin and review of the literature. *Pharmacotherapy* 2004; 24: 285–90.
8. Trilli LE, *et al.* Potential interaction between warfarin and fluvastatin. *Ann Pharmacother* 1996; 30: 1399–1402.
9. Kline SS, Harrell CC. Potential warfarin-fluvastatin interaction. *Ann Pharmacother* 1997; 31: 790–1.
10. Ahmad S. Lovastatin: warfarin interaction. *Arch Intern Med* 1990; 150: 2407.
11. Simonson SG, *et al.* Effect of rosuvastatin on warfarin pharmacodynamics and pharmacokinetics. *J Clin Pharmacol* 2005; 45: 927–34.
12. Barry M. Rosuvastatin–warfarin drug interaction. *Lancet* 2004; 363: 328.
13. Mondillo S, *et al.* Rosuvastatin–acenocoumarol interaction. *Clin Ther* 2005; 27: 782–4.
14. Hickmott H, *et al.* The effect of simvastatin co-medication on warfarin anticoagulation response and dose requirements. *Thromb Haemost* 2003; 89: 949–50.
15. Westergren T, *et al.* Probable warfarin–simvastatin interaction. *Ann Pharmacother* 2007; 41: 1292–5.
16. Grau E, *et al.* Simvastatin-oral anticoagulant interaction. *Lancet* 1996; 347: 405–6.

17. Jindal D, *et al.* Pharmacodynamic evaluation of warfarin and rosuvastatin co-administration in healthy subjects. *Eur J Clin Pharmacol* 2005; 61: 621–5.
18. Gew A, Wosornu D. Simvastatin during warfarin therapy in hyperlipoproteinaemia. *Lancet* 1992; 340: 979–80.
19. Binajat M, *et al.* Safety of the combination of intensive cholesterol-lowering therapy with oral anticoagulation medication in elderly patients with atrial fibrillation: a randomized, double-blind, placebo-controlled study. *Drugs Aging* 2009; 26: 585–93.
20. Trenque T, *et al.* Pravastatin: interaction with oral anticoagulant? *BMJ* 1996; 312: 886.
21. Schelleman H, *et al.* Fibrate/Statin initiation in warfarin users and gastrointestinal bleeding risk. *Am J Med* 2010; 123: 151–7.
22. Sconce EA, *et al.* The impact of simvastatin on warfarin disposition and dose requirements. *J Thromb Haemost* 2006; 4: 1422–4.
23. Inagaki Y, *et al.* Drug-drug interaction study to assess the effects of multiple-dose pitavastatin on steady-state warfarin in healthy adult volunteers. *J Clin Pharmacol* 2011; 51: 1302–9.
24. Owens JC, *et al.* Effect of sodium dextrothyroxine in patients receiving anticoagulants. *N Engl J Med* 1962; 266: 76–9.
25. Solomon HM, Schrogie JJ. Change in receptor site affinity: a proposed explanation for the potentiating effect of D-thyroxine on the anticoagulant response to warfarin. *Clin Pharmacol Ther* 1967; 8: 797–9.
26. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; 8: 70–7.
27. Robinson DS, *et al.* Interaction of warfarin and nonsystemic gastrointestinal drugs. *Clin Pharmacol Ther* 1971; 12: 491–5.
28. Jähnchen E, *et al.* Enhanced elimination of warfarin during treatment with cholestyramine. *Br J Clin Pharmacol* 1978; 5: 437–40.
29. Meinertz T, *et al.* Interruption of the enterohepatic circulation of phenprocoumon by cholestyramine. *Clin Pharmacol Ther* 1977; 21: 731–5.
30. Buckley MS, *et al.* Fish oil interaction with warfarin. *Ann Pharmacother* 2004; 38: 50–3.
31. McClaskey EM, Michalets EL. Subdural hematoma after a fall in an elderly patient taking high-dose omega-3 fatty acids with warfarin and aspirin: case report and review of the literature. *Pharmacotherapy* 2007; 27: 152–60.
32. Eritsland J, *et al.* Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coag Fibrinol* 1995; 6: 17–22.
33. Bender NK, *et al.* Effects of marine fish oils on the anticoagulation status of patients receiving chronic warfarin therapy. *J Thromb Thrombolysis* 1998; 5: 257–61.
34. De Witte P, Brems HM. Co-administration of benfluorex with oral anticoagulant therapy. *Curr Med Res Opin* 1980; 6: 478–80.
35. Harvengt C, Desager JP. Effect of colestipol, a new bile acid sequestrant, on the absorption of phenprocoumon in man. *Eur J Clin Pharmacol* 1973; 6: 19–21.

Menthol. Significant decreases in INR have been reported[1,2] in patients stabilised on warfarin when menthol cough preparations were taken.

1. Kassebaum PJ, *et al.* Possible warfarin interaction with menthol cough drops. *Ann Pharmacother* 2005; 39: 365–7.
2. Coderre K, *et al.* Probable warfarin interaction with menthol cough drops. *Pharmacotherapy* 2010; 30: 110.

Pesticides. Chlorinated insecticides diminished the activity of warfarin in a patient.[1]

1. Jeffery WH, *et al.* Loss of warfarin effect after occupational insecticide exposure. *JAMA* 1976; 236: 2881–2.

Piracetam. Piracetam caused an increase in prothrombin time in a patient who had been stabilised on warfarin.[1]

1. Pan HYM, Ng RP. The effect of Nootropil in a patient on warfarin. *Eur J Clin Pharmacol* 1983; 24: 711.

Sex hormones. There have been reports of steroids with anabolic or androgenic properties enhancing the activity of anticoagulants to the point of haemorrhage. Reports have covered *oxymetholone* and warfarin[1-3] or acenocoumarol;[4] *stanozolol* and warfarin[5,6] or dicoumarol;[7] *ethylestrenol* and phenindione;[8] *norethandrolone* and dicoumarol;[9] *methyltestosterone* and phenprocoumon;[10] and *danazol* and warfarin.[11-13] The manufacturer of *oxandrolone* states that an 80 to 85% reduction in warfarin dose was needed when oxandrolone was added to treatment. The mechanism of this interaction is not clear although it is considered that it is not caused by altered pharmacokinetics. Steroids with a 17-α-alkyl substituent appear to be most involved, but there has been a report of topically applied testosterone, which does not have such a substituent, enhancing warfarin.[14]

A retrospective study[15] of women receiving anticoagulant therapy who were started on *HRT* found that *tibolone* enhanced the effect of warfarin and of phenindione, possibly due to its androgenic properties. Tibolone again had a similar effect on warfarin in a prospective study in 16 healthy women.[16]

Oral contraceptives have also been implicated in interactions. However, while the effects of dicoumarol were diminished by a combined oral contraceptive,[17] those of acenocoumarol were enhanced by other preparations.[18] Combined oral contraceptives have increased the clearance of phenprocoumon without altering the anticoagulant effect.[19] There has also been a report[20] of a single course of *levonorgestrel* for emergency contraception increasing the effect of warfarin.

1. Robinson BHB, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; 1: 1356.
2. Longridge RGM, *et al.* Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; ii: 90.
3. Edwards MS, Curtis JR. Decreased anticoagulant tolerance with oxymetholone. *Lancet* 1971; ii: 221.
4. de Oya JC, *et al.* Decreased anticoagulant tolerance with oxymetholone in paroxysmal nocturnal haemoglobinuria. *Lancet* 1971; ii: 259.
5. Acomb C, Shaw PW. A significant interaction between warfarin and stanozolol. *Pharm J* 1965; 234: 73–4.
6. Shaw PW, Smith AM. Possible interaction of warfarin and stanozolol. *Clin Pharm* 1987; 6: 500–2.
7. Howard W, *et al.* Anabolic steroids and anticoagulants. *BMJ* 1977; 1: 1659–60.
8. Vere DW, Fearnley GR. Suspected interaction between phenindione and ethyloestrenol. *Lancet* 1968; ii: 281.
9. Schrogie JJ, Solomon HM. The anticoagulant response to bishydroxycoumarin: II. The effect of D-thyroxine, clofibrate, and norethandrolone. *Clin Pharmacol Ther* 1967; 8: 70–7.
10. Husted S, *et al.* Increased sensitivity to phenprocoumon during methyltestosterone therapy. *Eur J Clin Pharmacol* 1976; 10: 209–16.
11. Goulbourne IA, Macleod DAD. An interaction between danazol and warfarin: case report. *Br J Obstet Gynaecol* 1981; 88: 950–1.
12. Meeks ML, *et al.* Danazol increases the anticoagulant effect of warfarin. *Ann Pharmacother* 1992; 26: 641–2.
13. Booth CD. A drug interaction between danazol and warfarin. *Pharm J* 1993; 250: 439–40.
14. Lorentz SMcQ, Weibert RT. Potentiation of warfarin anticoagulation by topical testosterone ointment. *Clin Pharm* 1985; 4: 332–4.
15. McLintock LA, *et al.* Interaction between hormone replacement therapy preparations and oral anticoagulant therapy. *Br J Obstet Gynaecol* 2003; 110: 777–9.
16. Elbers J, *et al.* Tibolone (Livial) enhances warfarin-induced anticoagulation in postmenopausal women. *Maturitas* 2007; 56: 94–100.
17. Schrogie JJ, *et al.* Effect of oral contraceptives on vitamin K-dependent clotting activity. *Clin Pharmacol Ther* 1967; 8: 670–5.
18. de Teresa E, *et al.* Interaction between anticoagulants and contraceptives: an unsuspected finding. *BMJ* 1979; 2: 1260–1.
19. Mönig H, *et al.* Effect of oral contraceptive steroids on the pharmacokinetics of phenprocoumon. *Br J Clin Pharmacol* 1990; 30: 115–18.
20. Ellison J, *et al.* Apparent interaction between warfarin and levonorgestrel used for emergency contraception. *BMJ* 2000; 321: 1382.

St John's wort. St John's wort has been reported to reduce the anticoagulant effect of warfarin.[1]

1. Yue Q-Y, *et al.* Safety of St John's wort (Hypericum perforatum). *Lancet* 2000; 355: 576–7.

Thyroid and antithyroid drugs. Since response to oral anticoagulants is dependent on thyroid status an interaction between oral anticoagulants and thyroid or antithyroid drugs might be expected. Thyroid compounds do enhance the activity of oral anticoagulants possibly by increased metabolism of clotting factors. The effect of *dextrothyroxine* is discussed under Lipid Regulating Drugs, p. 1534.3. Antithyroid compounds have not, however, been reported to diminish the effect of anticoagulants and paradoxically *propylthiouracil* has been reported to have caused hypoprothrombinaemia (see Effects on the Blood, under Carbimazole, p. 2335.2). However, in a patient given *thiamazole* for Graves' disease, the response to warfarin varied depending on his thyroid status and thiamazole dose.[1]

1. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. *Ann Pharmacother* 2006; 40: 1200–3.

Tobacco. A systematic review and meta-analysis of 13 studies of the effects of smoking on warfarin[1] concluded that smoking can increase warfarin clearance, leading to reduced warfarin effects, thus smokers may need slightly higher doses; smoking cessation could therefore, conversely, enhance warfarin effects. Close monitoring of smoking status during warfarin therapy is advised.

1. Nathisuwan S, *et al.* Assessing evidence of interaction between smoking and warfarin: a systematic review and meta-analysis. *Chest* 2011; 139: 1130–9.

Ubidecarenone. Decreased INR values and reduced effect of warfarin have been reported[1] in 3 patients given ubidecarenone.

1. Spigset O. Reduced effect of warfarin caused by ubidecarenone. *Lancet* 1994; 344: 1372–3.

Vaccines. There have been a few reports of increased prothrombin time and bleeding in warfarin-stabilised patients after *influenza vaccination*; in 1 case a fatal intracranial bleed was possibly due to such an interaction.[1] However, studies have found only a small or inconsistent increase in warfarin activity[2,3] on vaccination, or no effect.[4-7] One study suggested that influenza vaccine decreased rather than increased the prothrombin time.[8] In a group of patients on long-term acenocoumarol therapy, influenza vaccination had no effect on acenocoumarol activity.[9]

1. Carroll DN, Carroll DG. Fatal intracranial bleed potentially due to a warfarin and influenza vaccine interaction. *Ann Pharmacother* 2009; 43: 754–60.
2. Kramer P, *et al.* Effect of influenza vaccine on warfarin anticoagulation. *Clin Pharmacol Ther* 1984; 35: 416–18.
3. Weibert RT, *et al.* Effect of influenza vaccine in patients receiving long-term warfarin therapy. *Clin Pharm* 1986; 5: 499–503.
4. Lipsky BA, *et al.* Influenza vaccination and warfarin anticoagulation. *Ann Intern Med* 1984; 100: 835–7.
5. Scott AK, *et al.* Lack of effect of influenza vaccination on warfarin in healthy volunteers. *Br J Clin Pharmacol* 1985; 19: 144P–145P.
6. Gomolin IH. Lack of effect of influenza vaccine on warfarin anticoagulation in the elderly. *Can Med Assoc J* 1986; 135: 39–41.
7. Iorio A, *et al.* Influenza vaccination and vitamin K antagonist treatment: a placebo-controlled, randomized, double-blind crossover study. *Arch Intern Med* 2010; 170: 609–16.
8. Bussey HI, Saklad JJ. Effect of influenza vaccine on chronic warfarin therapy. *Drug Intell Clin Pharm* 1988; 22: 198–201.
9. Souto JC, *et al.* Lack of effect of influenza vaccine on anticoagulation by acenocoumarol. *Ann Pharmacother* 1993; 27: 365–8.

Vitamins. Since vitamin K reverses the effects of oral anticoagulants, it is not surprising that there have been reports of *acetomenaphthone* and *phytomenadione* reducing anticoagulant activity, or of foods or nutritional preparations containing vitamin K compounds doing the same.

Occasional reports of *ascorbic acid* reducing the activity of warfarin[1,2] have not been confirmed in subsequent studies.[3,4] There have also been isolated reports suggesting that *vitamin E* may enhance the activity of warfarin[5] or dicoumarol,[6] although no effect was found in a study[7] of patients receiving warfarin and vitamin E. There has also been a report of elevated INR (greater than 12.3) in a patient on warfarin following the use of modified-release *nicotinamide*.[8]

1. Rosenthal G. Interaction of ascorbic acid and warfarin. *JAMA* 1971; 215: 1671.
2. Smith EC, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; 221: 1166.
3. Hume R, *et al.* Interaction of ascorbic acid and warfarin. *JAMA* 1972; 219: 1479.
4. Feetam CL, *et al.* Lack of a clinically important interaction between warfarin and ascorbic acid. *Toxicol Appl Pharmacol* 1975; 31: 544–7.
5. Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974; 230: 1300–1.
6. Schrogie JJ. Coagulopathy and fat-soluble vitamins. *JAMA* 1975; 232: 19.
7. Kim JM, White RH. Effect of vitamin E on the anticoagulant response to warfarin. *Am J Cardiol* 1996; 77: 545–6.
8. Christopher A. Critically elevated INR in a patient on warfarin after increase in extended-release niacin dose. *Ann Pharmacother* 2011; 45: e58.

Pharmacokinetics

Warfarin sodium is readily absorbed from the gastrointestinal tract; it can also be absorbed through the skin. It is extensively bound to plasma proteins and its plasma half-life is about 40 hours. It crosses the placenta but does not occur in significant quantities in breast milk. Warfarin is used as a racemic mixture; the *S*-isomer is more potent. The *R*- and *S*-isomers are both metabolised in the liver. The *S*-isomer is metabolised more rapidly than the *R*-isomer, mainly by the cytochrome P450 isoenzyme CYP2C9, which shows genetic polymorphism; other isoenzymes are also involved in the metabolism of the *R*-isomer. The stereoisomers may be affected differently by other drugs (see Interactions, p. 1529.3). Metabolites, with negligible or no anticoagulant activity, are excreted in the urine following reabsorption from the bile.

References.

1. Mungall DR, *et al.* Population pharmacokinetics of racemic warfarin in adult patients. *J Pharmacokinet Biopharm* 1985; 13: 213–27.
2. Holford NHG. Clinical pharmacokinetics and pharmacodynamics of warfarin: understanding the dose-effect relationship. *Clin Pharmacokinet* 1986; 11: 483–504.
3. Takahashi H, Echizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmacokinet* 2001; 40: 587–603.
4. Lane S, *et al.* The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors. *Br J Clin Pharmacol* 2012; 73: 66–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Circuvit; Coumadin; ***Austral.***: Coumadin; Marevan; ***Belg.***: Marevan; ***Braz.***: Coumadin; Marevan; Marfarin†; ***Canad.***: Coumadin; ***Chile***: Coumadin; ***Cz.***: Lawarin; ***Denm.***: Marevan; Waran; ***Fin.***: Marevan; ***Fr.***: Coumadine; ***Ger.***: Coumadin; ***Gr.***: Marevan; Panwarfin; ***Hung.***: Marfarin; ***India***: Uniwarfin; Warf; ***Indon.***: Simarc-2; ***Irl.***: Warfant; ***Israel***: Coumadin; ***Ital.***: Coumadin; ***Jpn***: Arefarin; Warlin; ***Malaysia***: Coumadin†; Orfarin; ***Mex.***: Coumadin; ***Norw.***: Marevan; ***NZ***: Coumadin; Marevan; ***Philipp.***: Coumadin; Warik; Zyfarin; ***Pol.***: Warfin; ***Port.***: Varfine; ***Rus.***: Marevan (Мареван); Warfarex (Варфарекс); ***Singapore***: Coumadin†; Marevan; Orfarin†; ***Spain***: Aldocumar; ***Swed.***: Waran; ***Thai.***: Befarin; Cogulax; Fargem; Maforan; Morfarin; Orfarin; Tufam†; Zydarin; ***Turk.***: Coumadin; Orfarin; ***UK***: Marevan; ***USA***: Coumadin; Jantoven; ***Venez.***: Anasmol; Coumadin; Cumar.

Pharmacopoeial Preparations

BP 2014: Warfarin Oral Suspension; Warfarin Tablets;
USP 36: Warfarin Sodium for Injection; Warfarin Sodium Tablets.

Xantinol Nicotinate (BAN, rINN)

Ksantinolinikotinaatti; Ksantynolu nikotynian; Nicotinato de xantinol; SK-331A; Xanthinol Niacinate (USAN); Xanthinol Nicotinate; Xanthinol nikotinát; Xantinol, Nicotinate de; Xantinol, nicotinato de; Xantinoli Nicotinas; Xantinolnikotinat; Ксантинола Никотинат.

7-[2-Hydroxy-3-[[2-hydroxyethyl)methylamino]propyl]theophylline nicotinate.

$C_{13}H_{21}N_5O_4.C_6H_5NO_2$=434.5

CAS — 437-74-1.

ATC — C04AD02.

The symbol † denotes a preparation no longer actively marketed

ATC Vet — QC04AD02.
UNII — 8G60H12X2D.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Xantinol nicotinate is a vasodilator with general properties similar to those of nicotinic acid (p. 2083.1), to which it is slowly hydrolysed. Xantinol nicotinate is used in the management of peripheral (p. 1272.3) and cerebral vascular disorders (p. 1269.2) and in hyperlipidaemias (p. 1248.1). Oral doses of up to 3 g daily may be given. It has also been given by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Ao Li Ao (奥利澳); Chang Long Qing (长龙清); Er Pu Mai (尔复迈); Fei Ke Mai Kang (菲克麦康); Fu Tong (孚通); Hai Fu Wei (海夫维); Hai Si Bi Da (海斯必达); He Xing (河星); Jingkang (靖康); Ni Pen Sa (尼芬萨); Qia Ke (恰克); Sai Tong (赛潼); Tai Wei Tong (太韦通); Tian Nuo Xin (天诺欣); Vedrin (爱全冬定); Xi Mei Xin (希美欣); Xin Pu Lu Tong (欣普路通); Yan Bi Er (延比尔); Yi Mei (怡玫); Yi Ting (怡汀); Zuo Nuo (左诺); Cz.: Xanidil†; *Ger.*: Complamin spezial†; *Hung.*: Xavin†; *India*: Complamina; *Neth.*: Complamin; *Pol.*: Sadamin†; *Rus.*: Xatinate (Ксатинат); *Switz.*: Complamin†.

Xemilofiban Hydrochloride *(USAN, rINNM)*

Hidrocloruro de xemilofibán; SC-54684A; Xémilofiban, Chlorhydrate de; Xemilofibán, hidrocloruro de; Xemilofibani Hydrochloridum; Ксемилофибана Гидрохлорид.

Ethyl (3*S*)-3-[3-[(*p*-amidinophenyl)carbamoyl]propionamido]-4-pentynoate monohydrochloride.

$C_{18}H_{22}N_4O_4HCl$=394.9

CAS — 149820-74-6 (xemilofiban); 156586-91-3 (xemilofiban hydrochloride).

UNII — HIU55WBI80.

Profile

Xemilofiban is a glycoprotein IIb/IIIa-receptor antagonist. It has been investigated as an oral antiplatelet drug for the management of thromboembolic disorders such as unstable angina, and after angioplasty, but results have been disappointing.

References.

1. O'Neill WW, *et al.* Long-term treatment with a platelet glycoprotein-receptor antagonist after percutaneous coronary revascularization. *N Engl J Med* 2000; 342: 1316–24.
2. Brugts JJ, *et al.* Relation of periprocedural bleeding complications and long-term outcome in patients undergoing percutaneous coronary revascularization (from the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events [EXCITE] Trial). *Am J Cardiol* 2009; 103: 917–22.

Xipamide *(BAN, USAN, rINN)* ⊗

Be-1293; Ksipamidi; MUF-10938; Xipamid; Xipamida; Xipamidum; Ксипамид.

4-Chloro-5-sulfamoylsalicylo-2',6'-xylidide; 5-(Aminosulphonyl)-4-chloro-*N*-(2,6-dimethylphenyl)-2-hydroxybenzamide.

$C_{15}H_{15}ClN_2O_4S$=354.8

CAS — 14293-44-8.

ATC — C03BA10.

ATC Vet — QC03BA10.

UNII — 459EYONUEC.

Uses and Administration

Xipamide is a diuretic, structurally related to indapamide, with actions and uses similar to those of the thiazide diuretics (see Hydrochlorothiazide, p. 1403.2). It is given orally for hypertension (p. 1251.1), and for oedema, including that associated with heart failure (p. 1262.3).

Diuresis begins about 1 or 2 hours after an oral dose, reaches a peak at 4 to 6 hours, and lasts for about 12 hours.

In the treatment of **hypertension** the usual dose is 20 mg daily as a single morning dose, either alone, or with other antihypertensives. In some patients a dose of 10 mg daily may be adequate. In the treatment of **oedema** the usual initial dose is 40 mg daily, subsequently reduced to 20 mg daily, according to response; in resistant cases 80 mg daily may be required.

References.

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; 30: 313–32.
2. Knauf H, Mutschler E. Zur Wirkungsweise von Xipamid und seiner Klassifizierung als "Low-ceiling-Diuretikum": pharmakodynamische und pharmakokinetische Untersuchungen an gesunden Probanden sowie bei Nieren- und Leberkranken. *Arzneimittelforschung* 2005; 55: 1–14.

Adverse Effects, Treatment, and Precautions

As for Hydrochlorothiazide, p. 1404.2.

Effects on electrolyte balance. Although reductions in plasma-potassium concentrations with xipamide have been shown to be on average comparable with those produced by thiazide and loop diuretics at equipotent doses,[1] there have been several reports of marked hypokalaemia in individual patients. Asymptomatic hypokalaemia was reported in 4 of 5 patients[2] (serum-potassium concentrations of less than 3.4 mmol/litre) and in 3 of 13 patients[3] (serum-potassium concentrations of less than 3.0 mmol/litre). Severe hypokalaemia resulting in ventricular arrhythmias has been reported after xipamide used alone[4] or with indapamide.[5] Profound electrolyte disturbances with altered consciousness and ventricular extrasystoles occurred in a patient taking digoxin after the addition of xipamide for 10 days.[6] A case of hypokalaemic periodic paralysis associated with xipamide use has also been reported.[7]

1. Prichard BNC, Brogden RN. Xipamide: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; 30: 313–32.
2. Weissberg P, Kendall MJ. Hypokalaemia and xipamide. *BMJ* 1982; 284: 975.
3. Raftery EB, *et al.* A study of the antihypertensive action of xipamide using ambulatory intra-arterial monitoring. *Br J Clin Pharmacol* 1981; 12: 381–5.
4. Altmann P, Hamblin JJ. Ventricular fibrillation induced by xipamide. *BMJ* 1982; 284: 494.
5. Boulton AJM, Hardisty CA. Ventricular arrhythmias precipitated by treatment with non-thiazide diuretics. *Practitioner* 1982; 226: 125–8.
6. Bentley J. Hypokalaemia and xipamide. *BMJ* 1982; 284: 975.
7. Boulton AJM, Hardisty CA. Hypokalaemic periodic paralysis precipitated by diuretic therapy and minor surgery. *Postgrad Med J* 1982; 58: 106–7.

Hepatic impairment. For a recommendation that xipamide should be given with caution to patients with liver disease, see under Pharmacokinetics, below.

Interactions

As for Hydrochlorothiazide, p. 1406.1.

Pharmacokinetics

Xipamide has been reported to be well absorbed from the gastrointestinal tract. Absorption is fairly rapid and peak plasma concentrations occur within 1 or 2 hours of oral doses. It is 99% bound to plasma proteins, and is excreted in the urine, partly unchanged and partly in the form of the glucuronide metabolite. It is reported to have a plasma half-life of about 5 to 8 hours. In patients with renal impairment excretion in the bile becomes more prominent.

References.

1. Beermann B, Grind M. Clinical pharmacokinetics of some newer diuretics. *Clin Pharmacokinet* 1987; 13: 254–66.

Hepatic impairment. Xipamide was present in the plasma and in ascitic fluid in patients with liver cirrhosis in proportion to the protein content of the respective compartments.[1] The amount of drug excreted into the urine was much greater in patients with liver disease than in healthy control subjects. This was attributed to a diminution in hepatic elimination, which could result in significant effects on the clinical response to xipamide. Thus patients with cholestasis could have an enhanced response to xipamide. On the other hand cirrhotic patients with the hepatorenal syndrome may be resistant to diuretics. Xipamide should be used with caution in patients with liver disease.

1. Knauf H, *et al.* Xipamide disposition in liver cirrhosis. *Clin Pharmacol Ther* 1990; 48: 628–32.

Renal impairment. After single oral and intravenous doses of xipamide 20 mg the drug appeared to be completely absorbed from the gastrointestinal tract.[1] The mean elimination half-life in healthy subjects was 7 hours and two-thirds of the clearance was by extrarenal routes. There was some accumulation in patients with chronic renal failure, with a calculated elimination half-life of 9 hours in end-stage renal disease.

1. Knauf H, Mutschler E. Pharmacodynamics and pharmacokinetics of xipamide in patients with normal and impaired kidney function. *Eur J Clin Pharmacol* 1984; 26: 513–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Aquaphoril; *Ger.*: Aquaphor; Aquex†; Xipa-Isis†; Xipa; Xipagamma; *India*: Xipamid; *Port.*: Diurexan; *Spain*: Diurex; *UK*: Diurexan; *Ukr.*: Xipagamma (Ксипогамма).

Multi-ingredient Preparations. *Ger.*: Neotri.

Zofenopril Calcium *(BANM, USAN, rINNM)*

Calcil Zofenoprilum; SQ-26991; Zofenopril cálcico; Zofénopril Calcique; Кальций Зофеноприл.

Calcium salt of (4*S*)-1-[(2*S*)-3-(Benzylthio)-2-methylpropionyl]-4-(phenylthio)-L-proline.

$C_{44}H_{44}CaN_2O_8S_4$=897.2

CAS — 81872-10-8 (zofenopril); 81938-43-4 (zofenopril calcium).

ATC — C09AA15.

ATC Vet — QC09AA15.

UNII — 88ZQ329PU2.

Profile

Zofenopril is an ACE inhibitor (p. 1282.2) that is used in the management of hypertension (p. 1251.1) and myocardial infarction (p. 1257.1). It owes its activity to the active metabolite zofenoprilat (SQ-26333) to which it is converted after oral doses. It is given orally in a usual daily maintenance dose of 30 to 60 mg of the calcium salt, as a single dose or in two divided doses.

References.

1. Ambrosioni E, *et al.* The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. *N Engl J Med* 1995; 332: 80–5.
2. Borghi C, *et al.* Effects of the administration of an angiotensin-converting enzyme inhibitor during the acute phase of myocardial infarction in patients with arterial hypertension: SMILE study investigators: Survival of Myocardial Infarction Long-term Evaluation. *Am J Hypertens* 1999; 12: 665–72.
3. Borghi C, *et al.* A review of the angiotensin-converting enzyme inhibitor, zofenopril, in the treatment of cardiovascular diseases. *Expert Opin Pharmacother* 2004; 5: 1965–77.
4. Buikema H. Use of the ACE inhibitor zofenopril in the treatment of ischemic heart disease. *Expert Rev Cardiovasc Ther* 2006; 4: 631–47.
5. Ambrosioni E. Defining the role of zofenopril in the management of hypertension and ischemic heart disorders. *Am J Cardiovasc Drugs* 2007; 7: 17–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Bifril; Zofenil; *Belg.*: Zopranol; *Chile*: Bifril†; *Fin.*: Bifril†; Zofenil; *Fr.*: Teoula; Zofenil; *Gr.*: Zofepril; Zopranol; *Irl.*: Zofenil; *Ital.*: Bifril; Zantipres; Zopranol; *Neth.*: Zofil; Zopranol; *Port.*: Zofenil; Zopranol; *Rus.*: Zocardis (Зокардис); *Singapore*: Bifril; *Switz.*: Zofenil†; *Turk.*: Zoprotec; *Ukr.*: Zocardis (Зокардис)†.

Multi-ingredient Preparations. *Austria*: Bifril Plus; Zofenil Plus; *Belg.*: Zopranol Plus; *Denm.*: Zofenil Comp; *Fin.*: Bifril Comp†; Zofenil Comp; *Fr.*: Coteoula; Zofenilduo; *Gr.*: Zofepril Plus; Zopranol Plus; *Irl.*: Zofenil Plus; *Ital.*: Bifrizide; Zantipride; Zopraziде; *Neth.*: Zofil HCTZ; Zopranol HCTZ; *Port.*: Zofenil Plus; Zopranol Plus; *Spain*: Zofenil Diu†; Zopranol Diu†; *Switz.*: Zofenil Plus†; *Turk.*: Zoprotec Plus; *Ukr.*: Zocardis Plus (Зокардис Плюс)†.

Chelators Antidotes and Antagonists

The drugs included in this chapter act in a variety of ways to counter the toxic effects of exogenous and endogenous substances in the body. They are therefore used in the management of poisoning and overdosage, to protect against the toxicity of drugs such as antineoplastics, and in the management of metabolic disorders such as Wilson's disease where toxic substances accumulate.

The main groups of drugs used include:

- antagonists, such as the opioid antagonist naloxone, that compete with the poison for receptor sites. Other antagonists act by blocking substances that mediate the effects of the toxin; atropine (p. 1310.2) acts in this way
- chelators and other drugs that form complexes with the toxin. This may reduce absorption of the toxin from the gastrointestinal tract, inactivate or reduce the activity of the toxin, or increase its elimination
- drugs that affect the metabolism of the toxin. Some antidotes, such as fomepizole in methyl alcohol poisoning, act by reducing the rate of metabolism to a toxic metabolite; alcohol (p. 1733.1) has a similar action. Others, such as methionine and glutathione, promote the formation of inactive metabolites; acetylcysteine (p. 1652.2) also acts in this way
- drugs that protect against the adverse effects of the toxin. Calcium folinate (p. 2066.3) is used for this purpose in methotrexate overdosage.

Acute poisoning

In the management of suspected acute poisoning it is often impossible to determine the identity of the poison or the size of the dose received with any certainty. Symptoms of acute poisoning are frequently non-specific, particularly in the early stages. Moreover, few poisons have specific antidotes or methods of elimination, and the mainstay of treatment for patients with suspected acute poisoning is therefore symptomatic and **supportive therapy**; in many cases nothing further is required. Supportive care in poisoning may include:

- maintenance of the airway, if necessary by intubation
- ensuring adequate ventilation
- managing shock or hypotension, mainly with intravenous fluids
- assessing consciousness and mental status and managing any immediate precipitating causes. Patients who are unconscious or who have respiratory depression may be given naloxone, particularly if opioid overdosage is a possibility. Some centres also recommend the routine administration of glucose to all unconscious patients since hypoglycaemia may be a cause of unconsciousness, although blood glucose measurements should be obtained first where facilities are immediately available
- monitoring for and controlling arrhythmias (although use of antiarrhythmic drugs may not be appropriate)
- monitoring for and controlling convulsions, usually with a benzodiazepine such as diazepam or lorazepam in the first instance
- managing hyper- or hypothermia with cooling measures or warming
- managing acidosis and fluid and electrolyte imbalances

Specific **antidotes** are available for several poisons and are the primary treatment where there is severe poisoning with a known toxin. They may be life-saving in such cases but their use is not without hazard and in many situations they are not necessary; their use should not preclude relevant supportive treatment.

Measures to reduce or **prevent absorption** of the poison are widely advocated. For inhalational poisoning the victim is removed from the source of poisoning. Some toxins, in particular pesticides, may be absorbed through the skin, and contaminated clothing should be removed and the skin thoroughly washed to avoid continued absorption. Caustic substances are removed from the skin or eyes with copious irrigation. However, for orally ingested poisons the best method for gastrointestinal decontamination remains controversial.

- *Activated charcoal* adsorbs various toxins and is often given to reduce absorption from the gastrointestinal tract.[1,2] A single dose is most likely to be effective if given as soon as possible after ingestion of a toxin, ideally within 1 hour.[1] Charcoal is generally well tolerated, although there is a risk of aspiration if the airway is not adequately protected. Repeated doses may be of use to eliminate some substances even after systemic absorption has occurred, such as those that undergo enterohepatic or enteroenteric recycling.[2]
- Active removal of poisons from the stomach by *induction of emesis* or *gastric lavage* has been widely used, but there is little evidence to support its role and there is potential for complications.[3-5]

  Induction of emesis with an emetic such as syrup of ipecacuanha has been used but is no longer recommended for either the home or hospital situation since there is no evidence that it improves outcomes, there are hazards associated with its use such as an increased risk of aspiration,[3,4] and it may delay the use or reduce the efficacy of activated charcoal, oral antidotes, and whole bowel irrigation.[3] If used at all, it should only be in fully conscious patients, where a potentially toxic amount has been ingested within the previous hour, and where other measures are unavailable or inappropriate. Emesis should not be induced if the poison is corrosive or petroleum based, if the toxin ingested is likely to alter mental status or cause seizures, or if the patient's condition may be adversely affected by vomiting.[3,4]

  Gastric lavage is also not recommended,[5] but may occasionally be considered for potentially life-threatening ingestion of non-caustic poisons that are not absorbed by activated charcoal, but only if less than one hour has elapsed since ingestion; it should not be attempted if the airway is not adequately protected or for petroleum-based toxins.
- *Cathartics* such as sorbitol or osmotic laxatives (such as magnesium citrate, magnesium sulfate, and sodium sulfate) have sometimes been used, but data do not support their use, either as the sole method of gut decontamination or routinely with activated charcoal.[6]
- *Whole-bowel irrigation* using a non-absorbable osmotic agent such as a macrogol has been used, particularly for substances that pass beyond the stomach before being absorbed, such as iron preparations or enteric-coated or modified-release formulations, but its role is not established.[7]
- Techniques intended to promote the elimination of poisons from the body, such as *haemodialysis* or *haemoperfusion*, are only of value for a limited number of poisons in a few severely poisoned patients.[8] *Forced diuresis* is no longer recommended, although *alkalinisation of the urine* using sodium bicarbonate infusion may have a role for selected poisons.[9]

Poisons Information Centres exist in many countries and should be consulted for more detailed information in specific situations; the International Programme on Chemical Safety has compiled a world directory of poisons centres (Yellow Tox).[10]

1. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clin Toxicol* 2005; **43**: 61–67. Also available at: http://www.clintox.org/documents/positionpapers/SingleDoseActivatedCharcoal.pdf (accessed 12/04/11)
2. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; **37**: 731–51. Also available at: http://www.clintox.org/documents/positionpapers/MultipleDoseActivatedCharcoal.pdf (accessed 12/04/11)
3. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: ipecac syrup. *J Toxicol Clin Toxicol* 2004; **42**: 133–43. Also available at: http://www.clintox.org/documents/positionpapers/IpecacSyrup.pdf (accessed 12/04/11) Correction. *ibid.*: 1000.
4. Manoguerra AS, Cobaugh DJ. Guidelines for the Management of Poisoning Consensus Panel. Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons. *Clin Toxicol* 2005; **43**: 1–10. Also available at: http://www.aapcc.org/archive/FinallizedPMGdlns/Ipecac%20Guideline%20-%20final%20for%20JTCT.pdf (accessed 12/04/11)
5. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. *J Toxicol Clin Toxicol* 2004; **42**: 933–43. Also available at: http://www.clintox.org/documents/positionpapers/GastricLavage.pdf (accessed 12/04/11)
6. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: cathartics. *J Toxicol Clin Toxicol* 2004; **42**: 243–53. Also available at: http://www.clintox.org/documents/positionpapers/Cathartics.pdf (accessed 12/04/11) Correction. *ibid.*: 1000.
7. American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position paper: whole bowel irrigation. *J Toxicol Clin Toxicol* 2004; **42**: 843–54. Also available at: http://www.clintox.org/documents/positionpapers/WholeBowelIrrigation.pdf (accessed 12/04/11) Correction. *ibid.*: 1000. [dose]
8. Greene SL, *et al.* Acute poisoning: understanding 90% of cases in a nutshell. *Postgrad Med J* 2005; **81**: 204–16.
9. Proudfoot AT, *et al.* American Academy of Clinical Toxicology. European Association of Poisons Centres and Clinical Toxicologists. Position Paper on urine alkalinization. *J Toxicol Clin Toxicol* 2004; **42**: 1–26. Also available at: http://www.clintox.org/documents/positionpapers/UrineAlkalinization.pdf (accessed 12/04/11)
10. International Programme on Chemical Safety. World directory of poisons centres (Yellow Tox). Available at: http://www.who.int/ipcs/poisons/centre/directory/en/ (accessed 05/05/11)

Activated Charcoal

Actieve Kool; A-Kohle; Aktif Kömür; Aktivihiili; Aktivsusi; Aktivált szén; Aktivkohle; Aktivt Kull; Aktyvintosios anglys; Carbó Actiu; Carbo Activatus; Carbo Medicinalis; Carbón activado; Carbone Attivo; Carvão Ativado; Charbon activé; Decolorising Charcoal; Kol, aktivt; Medicinal Charcoal; Uhlí aktivní; Węgiel leczniczy; Активен въглен; Активированный уголь.

CAS — 16291-96-6 (charcoal).
ATC — A07BA01.
ATC Vet — QA07BA01.
UNII — 2P3VWU3H10.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Charcoal, Activated). It is obtained from vegetable matter by suitable carbonisation processes intended to confer a high adsorption power. A black, light powder free from grittiness. Practically insoluble in all usual solvents. It adsorbs not less than 40% of its own weight of phenazone, calculated with reference to the dried substance. Store in airtight containers.

USP 36: (Activated Charcoal). The residue from the destructive distillation of various organic materials, treated to increase its adsorptive power. A fine, black, odourless, tasteless powder, free from gritty matter. The USP 36 has tests for adsorptive power in respect of alkaloids and dyes.

Uses and Administration

Activated charcoal can adsorb many plant and inorganic poisons including drugs such as salicylates, paracetamol, barbiturates, and tricyclic antidepressants; when given orally it reduces their systemic absorption from the gastrointestinal tract and is therefore used in the treatment of acute oral poisoning (p. 1538.1). It is of little value for poisoning with strong acids, alkalis, or other corrosive substances, alcohols, cyanides, clofenotane, malathion, petroleum distillates, and metals including iron, lithium, lead, sodium, potassium, magnesium, and mercury salts. Adsorption characteristics can be influenced by the charcoal's particle size, thus different responses may be obtained with different preparations.

Activated charcoal is given orally or via a nasogastric tube usually as a slurry in water. A usual dose for reduction of absorption is 50 g, but higher doses (100 g) have been used. For maximum efficacy, activated charcoal should be given as soon as possible (within 1 hour) after ingestion of the toxic compound. For some drugs such as those that undergo enterohepatic or enteroenteric recycling (e.g. phenobarbital and theophylline) *repeated doses* of activated charcoal are of value in enhancing faecal elimination. Doses for repeated administration in active elimination have varied but typically 50 g may be given every 4 hours; 25 g every 2 hours or 12.5 g hourly may be better tolerated, but efficacy may be affected. For doses in children, see p. 1538.1.

Mixtures such as 'universal antidote', which contained activated charcoal, magnesium oxide, and tannic acid, should not be used; activated charcoal alone is more effective and tannic acid may cause hepatotoxicity.

In treatment of poisoning using charcoal haemoperfusion, activated charcoal is used to remove drugs from the bloodstream. Where available, it may be of value in acute severe poisoning by drugs such as the barbiturates, carbamazepine or theophylline when other intensive measures fail to improve the condition of the patient.

Activated charcoal is used in dressings for ulcers and suppurating wounds (p. 1690.1) to absorb bacteria and reduce malodour.

Activated charcoal has been used as a marker of intestinal transit and has also been tried in the treatment of flatulence. Both activated charcoal and vegetable charcoal (wood charcoal; carbo ligni) are included in preparations for various gastrointestinal disorders.

Up to 1 mL of a suspension of activated charcoal 40 mg/mL may be injected subcutaneously after stereotactic or ultrasonic localisation of breast lesions to aid excision in subsequent surgery (within 60 days).

Technical grades of activated charcoal have been used as purifying and decolorising agents, for the removal of residual gases in low-pressure apparatus, and in respirators as a protection against toxic gases.

Administration. Activated charcoal is most commonly given as a slurry in water but this is often unpalatable because of the colour, gritty taste, lack of flavour, and dif-

ficulty in swallowing.[1] Flavourings and other excipients are often added in an attempt to improve palatability, although the effect of any additives on the adsorptive capacity of charcoal needs to be considered. Studies *in vitro* or in healthy subjects indicated that some foods such as ice cream, milk, and cocoa might inhibit the adsorptive capacity of activated charcoal, whereas starches and jams appeared to have no effect.[2,3] Carmellose has improved palatability although it might also reduce adsorptive capacity.[4-6] Saccharin sodium, sucrose, or sorbitol may be suitable additives,[7] although there may be problems associated with sorbitol-containing products (see under Poisoning, below). Chocolate syrup has also been used but the sweetness and flavour may disappear after a few minutes of contact with the activated charcoal.[1] The *BNFC* suggests that activated charcoal suspension may be mixed with soft drinks such as caffeine-free diet cola or fruit juices to mask the taste. A more recent study[8] of charcoal use in children with suspected poisoning found no evidence that use of flavourings improved the success of administration.

1. Scholtz BC, *et al.* Evaluation of five activated charcoal formulations for inhibition of aspirin absorption and palatability in man. *Am J Hosp Pharm* 1978; 35: 1355–9.
2. Levy G, *et al.* Inhibition by ice cream of the antidotal efficacy of activated charcoal. *Am J Hosp Pharm* 1975; 32: 289–91.
3. De Neve R. Antidotal efficacy of activated charcoal in presence of jam, starch and milk. *Am J Hosp Pharm* 1976; 33: 965–6.
4. Mathur LK, *et al.* Activated charcoal–carboxymethylcellulose gel formulation as an antidotal agent for orally ingested aspirin. *Am J Hosp Pharm* 1976; 33: 717–19.
5. Manes M. Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; 33: 1120, 1122.
6. Mathur LK, *et al.* Effect of carboxymethylcellulose on the adsorptive capacity of charcoal. *Am J Hosp Pharm* 1976; 33: 1122.
7. Cooney DO. Palatability of sucrose-, sorbitol-, and saccharin-sweetened activated charcoal formulations. *Am J Hosp Pharm* 1980; 37: 237–9.
8. Osterhoudt KC, *et al.* Activated charcoal administration in a pediatric emergency department. *Pediatr Emerg Care* 2004; 20: 493–8.

Administration in children. Activated charcoal is used in children for the treatment of acute oral poisoning. For the reduction of absorption of poisons, a usual dose is 1 g/kg (to a maximum of 50 g) given orally or via a nasogastric tube. This dose may be repeated every 4 hours for the active elimination of poisons. If vomiting is a problem, smaller amounts of charcoal given hourly or every 2 hours may cause less gastric irritation. The *BNFC* recommends these doses for neonates and children up to 12 years of age; thereafter usual adult doses may be used, see Uses and Administration, p. 1537.3.

Poisoning. The management of acute poisoning is discussed on p. 1537.1. The use of a *single oral dose* of activated charcoal has become a widespread method of preventing the absorption of ingested compounds and may be superior to gastric emptying. The American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) consider[1] that activated charcoal may be used if a patient presents within 1 hour of ingesting a potentially toxic amount of a poison known to be adsorbed by charcoal. There are insufficient data to support general use beyond 1 hour after ingestion.[1-3] A meta-analysis[4] of studies in healthy subjects found that although the reduction in drug exposure was optimal when activated charcoal was given immediately after drug intake, there was still some reduction in drug exposure when activated charcoal was given up to 4 hours after drug intake. It has been suggested that activated charcoal may be given several hours after poisoning with modified-release formulations or drugs that slow gastrointestinal transit such as antimuscarinics; however, the *National Poisons Information Service* in the UK considers that there is little evidence to support such use.

Multiple oral doses of activated charcoal have been found to enhance the elimination of some drugs and toxic substances even after systemic absorption. Mechanisms by which activated charcoal may increase drug elimination from the body include interruption of the enterohepatic circulation of drugs excreted into the bile, reduction of the reabsorption of drugs which diffuse or are actively secreted into the intestines, and increased elimination of the drug via the gastrointestinal tract when given with a laxative to decrease gastrointestinal transit time, although the practice of using charcoal with a laxative has been questioned.[5-7] Repeated oral doses of activated charcoal may therefore be considered for compounds that undergo enterohepatic or enteroenteric circulation, have a small volume of distribution, are not extensively bound to plasma proteins, and have a low endogenous clearance. A large study[8] in Sri Lanka found that routine treatment with multiple-dose activated charcoal was no better than no charcoal or just a single dose in reducing mortality from acute self-poisoning; the nature of the poison (mostly pesticides or oleander), time to presentation, or severity of symptoms did not alter the findings. However, it is unclear to what extent these results apply in other settings.[9] After a review of the literature[7] the AACT and EAPCCT recommended that multiple doses of charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. Anecdotal reports and studies in acutely poisoned patients indicate that a technique of giving multiple doses of charcoal may offer an alternative to charcoal haemoperfusion or haemodialysis. However, while activated charcoal is generally well tolerated, major complications do occasionally occur, including pulmonary aspiration and bowel obstruction.[10] Also, use of multiple doses of charcoal preparations containing sorbitol or sodium bicarbonate can result in increased vomiting[11] or in electrolyte disturbances.[9,12,13]

1. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *J Toxicol Clin Toxicol* 2005; 43: 61–87. Also available at: http://www.clintox.org/documents/positionpapers/SingleDoseActivatedCharcoal.pdf (accessed 10/05/11)
2. Green R, *et al.* How long after drug ingestion is activated charcoal still effective? *J Toxicol Clin Toxicol* 2001; 39: 601–5.
3. Cooper GM, *et al.* A randomized clinical trial of activated charcoal for the routine management of oral drug overdose. *Q J Med* 2005; 98: 655–60.
4. Jürgens G, *et al.* The effect of activated charcoal on drug exposure in healthy volunteers: a meta-analysis. *Clin Pharmacol Ther* 2009; 85: 501–5.
5. Neuvonen PJ, Olkkola KT. Oral activated charcoal in the treatment of intoxications: role of single and repeated doses. *Med Toxicol* 1988; 3: 33–58.
6. Neuvonen PJ, Olkkola KT. Effect of purgatives on antidotal efficacy of oral activated charcoal. *Hum Toxicol* 1986; 5: 255–63.
7. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *J Toxicol Clin Toxicol* 1999; 37: 731–51. Also available at: http://www.clintox.org/documents/positionpapers/MultipleDoseActivatedCharcoal.pdf (accessed 12/08/10)
8. Eddleston M, *et al.* Ox-Col Poisoning Study collaborators. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008; 371: 579–87.
9. Eyer P, Eyer F. Is this the epitaph for multiple-dose activated charcoal? *Lancet* 2008; 371: 538–9.
10. Palatnick W, Tenenbein M. Activated charcoal in the treatment of drug overdose: an update. *Drug Safety* 1992; 7: 3–7.
11. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; 27: 358–61.
12. McLuckie A, *et al.* Role of repeated doses of oral activated charcoal in the treatment of acute intoxications. *Anaesth Intensive Care* 1990; 18: 375–84.
13. Tenenbein M. Multiple doses of activated charcoal: time for reappraisal? *Ann Emerg Med* 1991; 20: 529–31.

HAEMOPERFUSION. Haemoperfusion involves the passage of blood through an adsorbent material such as activated charcoal or synthetic hydrophobic polystyrene resins that can retain certain drugs and toxic agents. Early problems with charcoal haemoperfusion such as charcoal embolism, marked thrombocytopenia, fibrinogen loss, and pyrogen reactions have been largely overcome by purification procedures and by coating the carbon with biocompatible polymers. However, transient falls in platelet count, leucocyte count, and circulatory concentrations of clotting factors, calcium, glucose, urea, creatinine, and urate have been reported during haemoperfusion. While there is no substitute for supportive measures, haemoperfusion can significantly reduce the body burden of certain compounds with a low volume of distribution within 4 to 6 hours in some severely poisoned patients; haemoperfusion is not effective for drugs or poisons with very large volumes of distribution. Use of haemoperfusion has declined in recent years in favour of improved haemodialysis techniques.

References.
1. Winchester JF. Dialysis and hemoperfusion in poisoning. *Adv Ren Replace Ther* 2002; 9: 26–30.
2. Holubek WJ, *et al.* Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int* 2008; 74: 1327–34.
3. Gil HW, *et al.* Clinical outcome of hemoperfusion in poisoned patients. *Blood Purif* 2010; 30: 84–8.

Porphyria. Activated charcoal may be used as part of the management of erythropoietic protoporphyria, one of the non-acute porphyrias (p. 1556.1). It acts as a sorbent in the gut lumen, interrupting the enterohepatic recycling of protoporphyrin. It may also have a role in congenital erythropoietic porphyria, a very rare porphyria. In a patient[1] with photomutilation due to this condition, activated charcoal 30 g given orally every 3 hours for 36 hours reduced the plasma-porphyrin concentration to normal values by 20 hours and was more effective than colestyramine or red cell transfusion. After stopping activated charcoal, plasma-porphyrin concentrations rose rapidly to near pretreatment levels within 10 days. Long-term treatment with oral charcoal over a 9-month period, at an optimal dose of 60 g three times daily, produced clinical remission with low concentrations of plasma and skin porphyrin and an absence of photocutaneous activity. However, exacerbation after an initial period of remission has been reported in another patient[2] and total lack of efficacy in a third.[3]

Activated charcoal has also been tried in variegate porphyria, but a study[4] in 8 patients found that oral charcoal led to clinical and biochemical deterioration with an increase in skin lesions and in urinary and plasma porphyrins.

1. Pimstone NR, *et al.* Therapeutic efficacy of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1987; 316: 390–3.
2. Hift RJ, *et al.* The effect of oral activated charcoal on the course of congenital erythropoietic porphyria. *Br J Dermatol* 1993; 129: 14–17.
3. Minder EI, *et al.* Lack of effect of oral charcoal in congenital erythropoietic porphyria. *N Engl J Med* 1994; 330: 1092–4.
4. Hift RJ, *et al.* Administration of oral activated charcoal in variegate porphyria results in a paradoxical clinical and biochemical deterioration. *Br J Dermatol* 2003; 149: 1266–9.

Pruritus. Activated charcoal has been tried in pruritus (p. 1687.3) associated with renal failure. In a double-blind crossover study,[1] activated charcoal 6 g daily orally for 8 weeks was more effective than placebo in relieving generalised pruritus in 11 patients undergoing maintenance haemodialysis. Another study[2] found that activated charcoal completely relieved pruritus in 10 of 23 haemodialysis patients, with a partial response in a further 10; treatment was generally well tolerated.

1. Pederson JA, *et al.* Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980; 93: 446–8.
2. Giovannetti S, *et al.* Oral activated charcoal in patients with uremic pruritus. *Nephron* 1995; 70: 193–6.

Tumour localisation. References to the use of injectable charcoal suspensions to localise lesions in the breast[1-4] and thyroid[5] for surgery.

1. Mullen DJ, *et al.* The use of carbon marking after stereotactic large-core-needle breast biopsy. *Radiology* 2001; 218: 255–60.
2. Ko K, *et al.* The value of ultrasound-guided tattooing localization of nonpalpable breast lesions. *Korean J Radiol* 2007; 8: 295–301.
3. Mathieu MC, *et al.* Tattooing breast cancers treated with neoadjuvant chemotherapy. *Ann Surg Oncol* 2007; 14: 2233–8.
4. Ruiz-Delgado ML, *et al.* Abnormal mammography and sonography associated with foreign-body giant-cell reaction after stereotactic vacuum-assisted breast biopsy with carbon marking. *Acta Radiol* 2008; 49: 1112–18.
5. Kang TW, *et al.* Preoperative ultrasound-guided tattooing localization of recurrences after thyroidectomy: safety and effectiveness. *Ann Surg Oncol* 2009; 16: 1655–9.

Adverse Effects and Precautions

Activated charcoal is relatively non-toxic when given orally but gastrointestinal disturbances such as vomiting, constipation, or diarrhoea have been reported. It may colour the faeces, tongue, and mucous membranes black. Activated charcoal should be used with caution in patients at risk of gastrointestinal obstruction as it may reduce gastrointestinal motility. It has been associated with intestinal obstruction and perforation after multiple dosing.

Care is needed if activated charcoal is used in patients receiving specific oral antidotes such as methionine (see Interactions, p. 1539.1). As with any treatment given orally for poisoning the risk of aspiration should be considered in drowsy or comatose patients.

The adverse effects of haemoperfusion with activated charcoal are similar to those of haemodialysis (see p. 1779.2); additionally, patients often develop thrombocytopenia, leucopenia, and hypocalcaemia. Charcoal embolism has also occurred. See also Haemoperfusion, above.

There may be local pain and stinging with subcutaneous use, and injection of volumes greater than 1 mL may result in leakage and spread into surrounding tissues. Granuloma and foreign body reactions have been reported occasionally when particles of activated charcoal were left in subcutaneous tissue for more than 6 months.

Effects on the gastrointestinal tract. Gastrointestinal adverse effects are the main complication of oral activated charcoal. Vomiting may occur and is a risk factor for pulmonary aspiration (see Effects on the Lungs, p. 1539.1). Although some preparations may cause diarrhoea, activated charcoal may reduce gastrointestinal motility and multiple doses have been associated with intestinal obstruction or faecal impaction,[1-4] in some cases leading to ulceration[5] or perforation;[6] overdosage with drugs that reduce gastrointestinal motility may increase the risk.[2,3,6] Perforation has occurred after a single dose in a patient with diverticular disease.[7] Two cases of pseudo-obstruction, one of which was fatal, have also been reported[8] after the use of activated charcoal and sorbitol with opioid sedation for theophylline poisoning. In another report,[9] severe peritonitis developed in a patient given oral activated charcoal after gastric lavage; charcoal was found in the peritoneum, although the site of perforation could not be detected. Acute appendicitis has also been reported after multiple doses of activated charcoal.[10]

1. Watson WA, *et al.* Gastrointestinal obstruction associated with multiple-dose activated charcoal. *J Emerg Med* 1986; 4: 401–7.
2. Anderson IM, Ware C. Syrup of Ipecacuanha. *BMJ* 1987; 294: 578.
3. Ray MJ, *et al.* Charcoal bezoar: small-bowel obstruction secondary to amitriptyline overdose therapy. *Dig Dis Sci* 1988; 33: 106–7.
4. Atkinson SW, *et al.* Treatment with activated charcoal complicated by gastrointestinal obstruction requiring surgery. *BMJ* 1992; 305: 563.
5. Mizutani T, *et al.* Rectal ulcer with massive haemorrhage due to activated charcoal treatment in oral organophosphate poisoning. *Hum Exp Toxicol* 1991; 10: 385–6.

6. Gomez HF, *et al.* Charcoal stercolith with intestinal perforation in a patient treated for amitriptyline ingestion. *J Emerg Med* 1994; 12: 57–60.
7. Green JP, McCauley W. Bowel perforation after single-dose activated charcoal. *CJEM* 2006; 8: 358–60.
8. Longdon P, Henderson A. Intestinal pseudo-obstruction following the use of enteral charcoal and sorbitol and mechanical ventilation with papavererum sedation for theophylline poisoning. *Drug Safety* 1992; 7: 74–7.
9. Mariani PJ, Pook N. Gastrointestinal tract perforation with charcoal peritoneum complicating orogastric intubation and lavage. *Ann Emerg Med* 1993; 22: 606–9.
10. Broglu A, *et al.* Multiple dose-activated charcoal as a cause of acute appendicitis. *J Toxicol Clin Toxicol* 2003; 41: 71–3.

Effects on the lungs. Vomiting after oral activated charcoal for acute poisoning has been associated with pulmonary aspiration of gastric contents, sometimes with fatal results.[1-3] Vomiting may be related to the formulation used and may be increased with sorbitol-containing preparations,[4] although a study in children[5] failed to confirm this. The use of a cuffed endotracheal tube has been recommended for any patient with impaired laryngeal reflexes to prevent aspiration;[3] however, there have been reports of aspiration despite a protected airway, including a case of obstructive laryngitis in a child.[6] Acute[7] and chronic[8] pulmonary toxicity has also been reported after accidental instillation of charcoal into the lung due to misplacement of the nasogastric tube.

1. Harsch HH. Aspiration of activated charcoal. *N Engl J Med* 1986; 314: 318.
2. Menzies DG, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; 297: 459–60.
3. Rau NR, *et al.* Fatal pulmonary aspiration of oral activated charcoal. *BMJ* 1988; 297: 918–19.
4. McFarland AK, Chyka PA. Selection of activated charcoal products for the treatment of poisonings. *Ann Pharmacother* 1993; 27: 358–61.
5. Osterhoudt KC, *et al.* Risk factors for emesis after therapeutic use of activated charcoal in acutely poisoned children. *Pediatrics* 2004; 113: 806–10.
6. Donoso A, *et al.* Activated charcoal laryngitis in an intubated patient. *Pediatr Emerg Care* 2003; 19: 420–1.
7. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med* 1993; 22: 1470–3.
8. Graff GR, *et al.* Chronic lung disease after activated charcoal aspiration. *Pediatrics* 2002; 109: 959–61.

Porphyria. Activated charcoal may be used in the management of some porphyrias (see p. 1538.2). The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies activated charcoal as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Activated charcoal has the potential to reduce the absorption of many drugs from the gastrointestinal tract and simultaneous oral therapy should therefore be avoided. In the management of acute poisoning, concurrent medication should be given parenterally. Care is needed if a specific oral antidote such as methionine is given since adsorption of the antidote may decrease its efficacy; it has been recommended that activated charcoal should be cleared from the stomach or avoided if oral antidotes are to be used. The adsorptive capacity of activated charcoal may be reduced by food, see Administration, p. 1537.3. Larger doses of activated charcoal may be needed if a large meal was eaten before treatment.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mamograf; Minicam Carb; *Austral.*: Ad-Sorb†; Carbonet; Carbosorb X; Charcocaps; Charcotabs; Charcotrace; *Austria*: Norit-Carbomix; Norit; *Belg.*: Carboflex; Carbonet; Charbogir; Charbon de Belloc; Norit-Carbomix; Norit; *Braz.*: Carverol; *Canad.*: Adsorba; Charac; Charcodote Aqueous; *Cz.*: Carbosorb; Norit†; *Denm.*: Norit Carbomix; *Fin.*: Adsorba C; Carbomix; *Fr.*: Carbactive; Carbomix; Carbonet; Charbon de Belloc; Colocarb†; Formocarbine; Splenocarbine; Toxicarb; *Ger.*: Adsorba C; Kohle-Compretten; Kohle-Hevert; Kohle-Pulvis; Kohle-Tabletten; Ultracarbon; *Gr.*: Carbomix†; Norit; Toxicarb; Ultracarbon; *Hong Kong*: Charcodote; *Hung.*: Cralex; *Indon.*: Bekarbon; *Irl.*: Carbomix; Carbonet; Liqui-Char; *Israel*: Norit; *Ital.*: Carbomix; *Malaysia*: Biocarbon; Ultracarbon; *Mex.*: Carbotural; *Neth.*: Norit; *Norw.*: Carbomix†; Kohle-Compretten; Kull; Medikol†; *NZ*: Carbosorb X; *Port.*: Carbomix; Norit; *Rus.*: Carbopekt (Карбопект); Ultra-Adsorb (Ультра-Адсорб); *Singapore*: Aqueous Charcodote; Norit†; Ultracarbon; *Spain*: Arkocapsulas Carbon Vegetal; Carbolig; Ultra Adsorb; *Swed.*: Carbomix; Kolsuspension; Medikol†; *Switz.*: Norit; *Thai.*: Ca-R-Bon; Deltacarbon; Ultracarbon; *Turk.*: Charflo Aqua; Farmacarbon; *UK*: Actidose-Aqua Advance; Adsorba C; Bragg's Medicinal Charcoal; Carbomix; Carbonet; Charcodote; Clinisorb; Legius; Lyofoam C; Modern Herbals Trapped Wind & Indigestion; Norit; *Ukr.*: Allocholum (Аллохол); Sorbex (Сорбекс); *USA*: Actidose-Aqua; Charcoaid†; Charcoal Plus; Charcocaps; EZ Char; Kerr Insta-Char; Liqui-Char.

Multi-ingredient Preparations. *Arg.*: Actisorb Plus; Carbogasol; Carbon Tabs; Diarrocalmol; Estreptocarbocaftiazol; Estreptocarbocaftiazol; Karbonetas†; Neoastrin; Opocarbon; *Austral.*: Carbosorb XS; *Austria*: Eucarbon; Intestinol†; *Belg.*: Carbobel; Carbolactanose; *Canad.*: Carboflex; Carbosylane; Charac Tol; Charcodote; *Chile*: Carbon Sulfaguanidina; *Cz.*: Carbocit; Carbotox; Eucarbon; *Fr.*: Acticarbine; Actisorb Ag*; Carbolevure; Carbophos; Carbosylane; Carbosymag; Notgaz†; Stomargil; *Ger.*: Mepilex Ag; *Gr.*: Carbosylane; *Hung.*: Eucarbon; *India*: Distenil; Enzolact; Gasnil; Intazyme; Jayzyme; Laxzyme; Medizyme; Nutrozyme; Papytazyme; Unienzyme; *Irl.*: Actisorb Silver; Carbosylane; *Israel*: Carbosylane; Charcodote; Eucarbon; Kaltocarb; Novicarbon†; *Ital.*: Actisorb; Carbone Composto†; Carbonesia; Carboyoghurt; Eucarbon; No-Gas; *Malaysia*: Eucarbon Herbal; Eucarbon; *Mex.*: Acilin; Dipecfur; *NZ*: Carbosorb XS; *Pol.*: Rapacholin AC†; Rapacholin C; *Rus.*: Unienzyme с MPS (Юнензим с МПС); *S.Afr.*: Eucarbon†; *Singapore*: Charcodote; *Switz.*: Carbolevure; Carboticon; Carvon; *Thai.*: Belacid; Bicobon; Biodan; Carbomint; Carbonpectate; Delta Charcoal; Pepsitase; Polyenzyme-I†; Pro ABS; *Turk.*: Charflo Sorbitol†; Eucarbon; Intestinol; Karboseptin; *UK*: Acidosis; Actisorb Silver; Carbellon; Thickhead; *Ukr.*: Eucarbon (Эукарбон); Huato Pills (Болюсы Хуато); *USA*: Actidose with Sorbitol; Flatulex†; Poison Antidote Kit; *Venez.*: Carbargal con Atropina; Carbargal; Guanicar.

Homoeopathic Preparations. *Austral.*: Elimitona Slim & Detox; Elimitona; IBS Eze; Stomach Calm; Vitatona Energy†; *Austria*: Gastricumeel; Katerex; *Canad.*: Bioactiv N†; Cocyntal; Cruroheel S†; Endoteel†; Erysidoron 2†; Formula BS 211; Formula Homeo QR 209†; Gastrosine†; Hylands Upset Stomach; Ikoplex 11 Digestion Aid†; Ind Complex†; *Chile*: Bioactiv N; Similibus; *Cz.*: Gastrocynesine; *Fr.*: Abbe Chaupitre no 44†; Cina Compose; Dermo-Drainol†; Gastro-Drainol†; Gastrocynesine; Veino-Drainol†; Voxpax; *Ger.*: Carminativum Hevert; Derivatio H; Derivatio; EAP-61; gastri-loges N; Gastritis Complex; Gastro Magentabletten; Infi-Camphora; Infihepan; Lowe-Komplex Nr 6; Nuxal comp; Nuxal H; Sinuselect N; Stoma-Gastreu S R5; *Neth.*: Chavita 1; Gastricumeel; Gastrocynesine†; Okugest; *Port.*: Gastrocynesine; *Rus.*: Capsicum-Plus (Капсикум-Плюс); *Switz.*: Exsepta; Gastricumeel; Omida comprimes homeopathiques pour la gorge; Regenaplex Nr. 59b.

Amifostine *(BAN, USAN, rINN)*

Amifostiini; Amifostin; Amifostina; Amifostinum; Ethiofos; Gammaphos; NSC-296961; WR-2721; Амифостин.

S-[2-(3-Aminopropylamino)ethyl] dihydrogen phosphorothioate.

$C_5H_{15}N_2O_3PS$=214.2

CAS — 20537-88-6 (amifostine); 63717-27-1 (amifostine monohydrate); 112901-68-5 (amifostine trihydrate).

ATC — V03AF05.

ATC Vet — QV03AF05.

UNII — ILA426L95O (amifostine); L693H6MM64 (amifostine monohydrate); M487QF2F4V (amifostine trihydrate).

Pharmacopoeias. *US* includes the trihydrate.

USP 36: (Amifostine). The trihydrate is a white crystalline powder. Freely soluble in water. pH of a 5% solution in water is between 6.5 and 7.5. Store in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

Incompatibility. Amifostine has been reported[1] to be physically incompatible with aciclovir sodium, amphotericin B, cefoperazone sodium, chlorpromazine hydrochloride, cisplatin, ganciclovir sodium, hydroxyzine hydrochloride, miconazole, minocycline hydrochloride, and prochlorperazine edisilate during simulated Y-site administration.

1. Trissel LA, Martinez JF. Compatibility of amifostine with selected drugs during simulated Y-site administration. *Am J Health-Syst Pharm* 1995; 52: 2208–12.

Uses and Administration

Amifostine, an aminothiol compound, is a cytoprotective agent (see also below). It is converted in the body to its active metabolite WR-1065, which protects noncancerous cells against the toxic effects of antineoplastics and ionising radiation. It is used to reduce neutropenia-related infection associated with cyclophosphamide and cisplatin therapy and to reduce the cumulative renal toxicity associated with repeated cisplatin use. It is also used to reduce the incidence of xerostomia (dry mouth) in patients undergoing radiation therapy for head and neck cancer. Licensing details may vary between countries. Amifostine is under investigation in ameliorating the adverse effects of other antineoplastics and in the treatment of myelodysplasia.

In chemotherapy, amifostine is given by intravenous infusion over 15 minutes starting no more than 30 minutes before the antineoplastic therapy at a usual dose of 910 mg/m² once daily. Subsequent doses should be reduced to 740 mg/m²(or 728 mg/m² in some countries) in patients unable to tolerate the full dose. A dose of 740 mg/m² is recommended for the reduction of cisplatin toxicity if doses of cisplatin of less than 100 mg/m² are used.

In the prevention of xerostomia, amifostine is given in a dose of 200 mg/m² daily as a 3-minute intravenous infusion starting 15 to 30 minutes before radiotherapy.

For use in children, see below.

Administration in children. Amifostine has been investigated as a cytoprotectant in children with variable results. In children from 3 years of age given a high-dose cisplatin regimen for medulloblastoma, intravenous amifostine 600 mg/m² given over 1 minute before and 3 hours into each cisplatin infusion significantly reduced grade 3 and 4 ototoxicity without altering outcomes after 1 year.[1] Earlier studies have also reported successful use of adult doses of amifostine (see above) in children on platinum regimens for solid tumours.[2,3] However, a reduction in cisplatin toxicity has not been seen in some other studies in osteosarcoma[4] and germ-cell tumours.[5]

Amifostine has also been tried subcutaneously as a radioprotectant in small numbers of children.[6]

1. Fouladi M, *et al.* Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma. *J Clin Oncol* 2008; 26: 3749–55.
2. Stolarska M, *et al.* Cytoprotective effect of amifostine in the treatment of childhood neoplastic diseases—a clinical study including the pharmacoeconomic analysis. *Pharmacol Rep* 2006; 58: 30–4.
3. Sidi V, *et al.* Use of amifostine in the treatment of recurrent solid tumours in children. *Hippokratia* 2007; 11: 25–9.
4. Gallegos-Castorena S, *et al.* Toxicity prevention with amifostine in pediatric osteosarcoma patients treated with cisplatin and doxorubicin. *Pediatr Hematol Oncol* 2007; 24: 403–8.
5. Marina N, *et al.* Children's Oncology Group. Amifostine does not protect against the ototoxicity of high-dose cisplatin combined with etoposide and bleomycin in pediatric germ-cell tumors: a Children's Oncology Group study. *Cancer* 2005; 104: 841–7.
6. Anacak Y, *et al.* Daily subcutaneous amifostine administration during irradiation of pediatric head and neck cancers. *Pediatr Blood Cancer* 2007; 48: 579–81.

Cytoprotection. WR-1065, the active metabolite of amifostine, readily enters non-malignant cells where it deactivates cytotoxics such as alkylating and platinum-containing antineoplastics and protects against the effects of ionising radiation.[1-3] The cytoprotective effects of amifostine are reported to be selective for normal cells and not to interfere with the cytotoxic effects of antineoplastics and radiation on malignant cells. Several factors contribute to this selectivity, including the lower alkaline phosphatase content of malignant cells compared with normal cells, and the lower pH of malignant tissues, both of which decrease the formation and uptake of WR-1065 by malignant cells.[2,3]

Benefit has been reported with amifostine in various malignancies and the American Society of Clinical Oncology currently recommends[4] that its use may be considered for the prevention of nephrotoxicity in patients receiving cisplatin-based chemotherapy, as a treatment option for the reduction of severe neutropenia associated with chemotherapy, or to decrease the incidence of xerostomia in patients receiving radiotherapy alone for head and neck cancer. However, a systematic review[5] of 2 studies found amifostine had no radioprotective effect on the salivary glands in patients with differentiated thyroid cancer treated with high-dose radio-iodine.

Amifostine has been tried for mucositis and may be effective at preventing radiation proctitis in those receiving standard-dose radiotherapy for rectal cancer;[6] a dose of at least 340 mg/m² has been suggested, given before radiotherapy (see also Mucositis, p. 732.1).

Although amifostine is licensed for intravenous use, other routes have been tried.[7] The subcutaneous route is frequently tried, most often in a dose of 500 mg before radiotherapy, and has generally been found to be effective and associated with fewer adverse effects. Although it may offer advantages over intravenous use in terms of ease of administration and compliance, this has been contested by some.[7,8] Amifostine has also been tried rectally and as orally-active modified-release nanoparticles.[7]

Amifostine has also been used in children, see Administration in Children, above.

1. Foster-Nora JA, Siden R. Amifostine for protection from antineoplastic drug toxicity. *Am J Health-Syst Pharm* 1997; 54: 787–800.
2. Mabro M, *et al.* A risk-benefit assessment of amifostine in cytoprotection. *Drug Safety* 1999; 21: 367–87.
3. Culy CR, Spencer CM. Amifostine: an update on its clinical status as a cytoprotectant in patients with cancer receiving chemotherapy or radiotherapy and its potential therapeutic application in myelodysplastic syndrome. *Drugs* 2001; 61: 641–84.
4. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; 27: 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 13/05/11)
5. Ma C, *et al.* Amifostine for salivary glands in high-dose radioactive iodine treated differentiated thyroid cancer. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 13/05/11).
6. Keefe DM, *et al.* Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007; 109: 820–31.
7. Praetorius NP, Mandal TK. Alternate delivery route for amifostine as a radio-/chemo-protecting agent. *J Pharm Pharmacol* 2008; 60: 809–15.
8. Bardet E, *et al.* Subcutaneous compared with intravenous administration of amifostine in patients with head and neck cancer receiving radiotherapy: final results of the GORTEC 2000-02 phase III randomized trial. *J Clin Oncol* 2011; 29: 127–33.

Adverse Effects, Treatment, and Precautions

Amifostine may cause a transient reduction, usually in systolic, or, less frequently, in diastolic blood pressure. However, more pronounced reductions in blood pressure may occur and transient loss of consciousness has been reported very rarely. To minimise hypotension, patients should be adequately hydrated before treatment begins and should be in a supine position. Amifostine should not be used in patients who are hypotensive or dehydrated. Patients taking antihypertensive drugs should stop treatment 24 hours before starting amifostine. Arterial blood pressure must be monitored during the amifostine infusion and if systolic blood pressure decreases significantly, the infusion must stop. Hypotension should be managed with infusion of sodium chloride 0.9% and postural management. Amifostine may be continued if blood pressure returns to normal within 5 minutes. If the full dose cannot be given, a reduced dose of amifostine is used for subsequent chemotherapy cycles, see Uses and Administration, p. 1539.2.

Tachycardia or bradycardia, arrhythmias, chest pain, myocardial ischaemia, myocardial infarction, cardiac arrest, convulsions, dyspnoea, apnoea, hypoxia, respiratory arrest, and renal failure have occurred rarely, and may be associated with hypotension. Caution is required in patients with cardiovascular or cerebrovascular disease, in elderly patients, and in those at risk of renal impairment.

Nausea and vomiting are common and use with an antiemetic is recommended.

Amifostine reduces serum-calcium concentrations, although clinical hypocalcaemia has occurred only very rarely. Serum-calcium concentrations should be monitored in patients at risk of hypocalcaemia and calcium supplements given if needed.

Other adverse effects include flushing, chills, fever, dizziness, somnolence, hiccups, and sneezing. Hypersensitivity reactions and anaphylactoid reactions have been reported including pruritus, urticaria, chest tightness, and laryngeal oedema. Amifostine should be immediately and permanently stopped if a severe acute allergic reaction occurs. Rashes may occur and there have been reports of more severe skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, and bullous toxicity; fatalities have occurred. Most reactions developed after 10 or more days of amifostine treatment as a radioprotectant. Amifostine should be withheld if a cutaneous reaction occurs, and stopped permanently for serious or severe reactions, or if the reaction is associated with other symptoms such as fever.

Giving amifostine over a longer period than 15 minutes is associated with a higher incidence of adverse effects.

References.
1. Boccia R, *et al.* Assessment and management of cutaneous reactions with amifostine administration: findings of the ethyol (amifostine) cutaneous treatment advisory panel (ECTAP). *Int J Radiat Oncol Biol Phys* 2004; **60**: 302–9.

Effects on the musculoskeletal system. Shortly after an amifostine injection into the upper arm, a patient reported severe pain radiating from the injection site to the shoulders, neck, back, and waist, with numbness of the upper arms.[1]

1. Morales G, *et al.* Amifostine-induced back pain: a case report. *Am J Health-Syst Pharm* 2006; **63**: 381–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies amifostine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Antihypertensives may potentiate hypotension caused by amifostine and it is therefore recommended that they be stopped 24 hours before starting amifostine treatment.

Pharmacokinetics

Amifostine is rapidly cleared from the plasma after intravenous doses and is dephosphorylated by alkaline phosphatase to the active metabolite WR-1065, a free thiol compound. This is further metabolised to a less active disulfide metabolite (WR-33278). The elimination half-life of amifostine after a 15-minute infusion is less than 10 minutes. Renal excretion of amifostine and its metabolites is minimal.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Erifostine; *Austral.*: Ethyol; *Belg.*: Ethyol; *Braz.*: Ethyol; *Chile*: Ethyol†; *China*: An Fu Ding (安福定); Cytofos (采福); Tian Di Da (天地达); *Cz.*: Ethyol; *Fin.*: Ethyol; *Fr.*: Ethyol; *Ger.*: Ethyol†; *Gr.*: Ethyol; *India*: Amfos; Amiphos; Cytofos; Ethyol; M-Fost; Naprofos; *Israel*: Ethyol†; *Ital.*: Ethyol; *Mex.*: Ethyol; *Neth.*: Ethyol; *NZ*: Ethyol; *Philipp.*: Ethyol; *Pol.*: Ethyol†; *Port.*: Ethyol; *Rus.*: Ethyol (Этиол); *S. Afr.*: Ethyol; *Spain*: Ethyol; *Swed.*: Ethyol; *Switz.*: Ethyol; *Thai.*: Cytofos; Ethyol; *Turk.*: Ethyol; *UK*: Ethyol; *USA*: Ethyol; *Venez.*: Ethyol.

Pharmacopoeial Preparations
USP 36: Amifostine for Injection.

Ammonium Tetrathiomolybdate

Tetratiomolibdato de amonio.
$(NH_4)_2MoS_4$=260.3
CAS — 15060-55-6.
UNII — 4V6I63LW1E

NOTE. The name Coprexa has been used as a trade mark for ammonium tetrathiomolybdate.

Profile

Ammonium tetrathiomolybdate is a chelator that aids the elimination of copper from the body. It is under investigation in the treatment of Wilson's disease and pulmonary fibrosis. There is also some interest in its use in the treatment of malignant neoplasms.

References.
1. Medici V, Sturniolo GC. Tetrathiomolybdate, a copper chelator for the treatment of Wilson disease, pulmonary fibrosis and other indications. *IDrugs* 2008; **11**: 592–606.
2. Brewer GJ. The use of copper-lowering therapy with tetrathiomolybdate in medicine. *Expert Opin Invest Drugs* 2009; **18**: 89–97.
3. Khan G, Merajver S. Copper chelation in cancer therapy using tetrathiomolybdate: an evolving paradigm. *Expert Opin Invest Drugs* 2009; **18**: 541–8.

Wilson's disease. Ammonium tetrathiomolybdate forms a complex with protein and copper. When it is taken with food it blocks the intestinal absorption of copper, and when given between meals it combines with albumin- and caeruloplasmin-bound copper. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels in patients with Wilson's disease (p. 1567.3); it may be particularly suitable for patients with neurological symptoms.[1] Bone marrow depression[1,2] and raised liver enzymes[1] have been reported; both have responded to temporary withdrawal or dose reduction.

1. Brewer GJ, *et al.* Treatment of Wilson disease with ammonium tetrathiomolybdate III: initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. *Arch Neurol* 2003; **60**: 379–85.
2. Harper PL, Walshe JM. Reversible pancytopenia secondary to treatment with tetrathiomolybdate. *Br J Haematol* 1986; **64**: 851–3.

Amyl Nitrite

Amile Nitrito; Amil-nitrit; Amyli Nitris; Amylis Nitris; Amylium Nitrosum; Amylnitrit; Amylnitritt; Amyylinitriitti; Azotito de Amilo; Azotyn Amylu; Dusitan Amylnatý; Isoamyl Nitrite; Isoamylnitriet; Isoamyylinitriitti; Isopentyl Nitrite; Isopentylnitrit; Nitrite d'amyle; Nitrito de Amila; Nitrito de amilo; Nitrito di Amile; Pentanolis Nitris; Нитрит Амила; Амилнитрит; Амілнітрит.

$C_5H_{11}NO_2$=117.1
ATC — V03AB22.
ATC Vet — QV03AB22.
UNII — 22T8Z09XAK (amyl nitrite); 5N0U5TUC9Z (3-methyl-1-butanol).

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of amyl nitrite:

60 second trip; Aimes; Aimies; Ames; Amys; Boppers; Hard on; Pearls; Poppers; Sixty second trip; Snappers; Whiffenpoppers.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Amyl Nitrite). A mixture of the nitrite esters of 3-methyl-1-butanol and 2-methyl-1-butanol. A clear, yellowish liquid having a pecullar, ethereal, fruity odour. It is very flammable. It is volatile even at low temperatures. B.p. about 96 degrees. Practically insoluble in water; miscible with alcohol and with ether. Store in a cool place in airtight containers. Protect from light.

Stability. Amyl nitrite is liable to decompose with evolution of nitrogen, particularly if it has become acid in reaction.

Uses and Administration

Amyl nitrite is rapidly absorbed on inhalation and is used in the immediate treatment of patients with definite cyanide poisoning (p. 2156.2) to induce the formation of methaemoglobin, which combines with the cyanide to form non-toxic cyanmethaemoglobin. Other mechanisms such as nitric oxide formation, vasodilatation, and improved hepatic blood flow may also contribute to its mode of action. A suggested procedure is to give amyl nitrite by inhalation for up to 30 seconds every minute until intravenous treatment with sodium nitrite (p. 1574.3) and sodium thiosulfate (p. 1576.2) can be started. It has also been suggested for use in the management of hydrogen sulfide poisoning (p. 1799.2).

Amyl nitrite has an action similar to that of glyceryl trinitrate (p. 1391.3) and used to be given by inhalation for the relief of acute attacks of angina pectoris but is seldom used now.

Homoeopathy

Amyl nitrite has been used in homoeopathic medicines under the following names: Amyl nitrosum; Am. nit.; Amyl nit.

Uterine relaxation. Amyl nitrite relaxes uterine smooth muscle. While it is no longer used as a tocolytic, amyl nitrite inhalation has been used during labour to facilitate preterm caesarean section,[1] with general anaesthesia to relax uterine constriction rings,[2] or with epidural anaesthesia in the management of shoulder dystocia.[3]

1. Hendricks SK, *et al.* Amyl nitrite: use as a smooth muscle relaxant in difficult preterm cesarean section. *Am J Perinatol* 1992; **9**: 289–92.
2. El-Mowalfi DM. Geneva Foundation for Medical Education and Research. *Obstetrics simplified*: abnormal uterine action. Available at: http://www.gfmer.ch/Obstetrics_simplified/abnormal_uterine_action.htm (accessed 11/01/11)
3. Hepner DL, *et al.* The Zavanelli maneuver does not preclude regional anesthesia. *Anesth Analg* 1997; **84**: 1145–6.

Adverse Effects, Treatment, and Precautions

Amyl nitrite inhalation commonly causes flushing, headache, and dizziness; nausea and vomiting, hypotension, restlessness, pallor, sweating, urinary and faecal incontinence, and tachycardia may also occur. Overdosage may result in cyanosis, syncope, dyspnoea, and muscular weakness, due to vasodilatation and methaemoglobinaemia. Methylthioninium chloride may be required for severe methaemoglobinaemia but should not be used if cyanide poisoning is suspected since cyanide may be displaced. Respiratory depression, metabolic acidosis, convulsions, coma, and cardiovascular collapse can occur in severe toxicity; deaths are very rare.

Amyl nitrite may increase intra-ocular and intracranial pressure and should be used with caution in patients with glaucoma, recent head trauma, or cerebral haemorrhage.

Tolerance to nitrites can develop with chronic use.

Abuse. Volatile alkyl nitrites (commonly known as 'poppers'), including amyl, butyl, or isobutyl nitrite, have been abused in the belief that they expand creativity, stimulate music appreciation, promote a sense of abandon in dancing, and intensify sexual experience.[1,2]

Inhalation causes headache, tachycardia, syncope, acute psychosis, increased intra-ocular pressure, transient hemiparesis, methaemoglobinaemia, coma, and, rarely, sudden death. Haemolytic anaemia has also been reported[3-7] and may be more likely in those with glucose-6-phosphate deficiency;[5,7] in some subjects, Heinz body formation has been detected.[3,6] Methaemoglobinaemia may be severe,[8] and has also been reported after ingestion of volatile nitrites.[9-12] Symptoms are similar to those of hypoxia[11] and may be reversed by methylthioninium chloride.[8-12] Bilateral vision loss has been reported due to damage to the foveal photoreceptors; in some patients symptoms improved over several weeks.[13,14]

Inhalation of volatile nitrites has led to severe and extensive contact dermatitis around the face with secondary spread elsewhere on the body.[15,16]

1. Sigell LT, *et al.* Popping and snorting volatile nitrites: a current fad for getting high. *Am J Psychiatry* 1978; **135**: 1216–18.
2. Lockwood B. Poppers: volatile nitrite inhalants. *Pharm J* 1996; **257**: 154–5.
3. Romeril KR, Concannon AJ. Heinz body haemolytic anaemia after sniffing volatile nitrites. *Med J Aust* 1981; **1**: 302–3.
4. Brandes JC, *et al.* Amyl nitrite-induced hemolytic anemia. *Am J Med* 1989; **86**: 252–4.
5. Graves TD, Mitchell S. Acute haemolytic anaemia after inhalation of amyl nitrite. *J R Soc Med* 2003; **96**: 594–5.
6. Shortt J, *et al.* Oxidative haemolysis due to 'poppers'. *Br J Haematol* 2008; **142**: 328.
7. Neuberger A, *et al.* Hemolytic anemia in a G6PD-deficient man after inhalation of amyl nitrite ('poppers'). *Isr Med Assoc J* 2002; **4**: 1085–6.
8. Modarai B, *et al.* Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. *Emerg Med J* 2002; **19**: 270–1.
9. Lasbaa JP, *et al.* Amyl nitrite poppers and methemoglobulinemia. *Ann Intern Med* 1985; **103**: 804–5.
10. Osterloh J, Olson K. Toxicities of alkyl nitrites. *Ann Intern Med* 1986; **104**: 727.
11. Pierce JMT, Nielsen MS. Acute acquired methaemoglobinaemia after amyl nitrite poisoning. *BMJ* 1989; **298**: 1566.
12. Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. *Arch Dis Child* 1991; **66**: 152.
13. Pece A, *et al.* Transient visual loss after amyl isobutyl nitrite abuse. *Semin Ophthalmol* 2004; **19**: 105–6.
14. Vignal-Clermont C, *et al.* Poppers-associated retinal toxicity. *N Engl J Med* 2010; **363**: 1583–5.

15. Bos JD, *et al.* Allergic contact dermatitis to amyl nitrite ('poppers'). *Contact Dermatitis* 1985; 12: 109.
16. Forozan M, *et al.* Dermatose faciale aux poppers. *Ann Dermatol Venereol* 2009; 136: 298–9.

Handling and storage. Amyl nitrite is very flammable and must not be used where it may be ignited. It should be protected from light.

Pregnancy. Licensed product information warns that maternal use of amyl nitrite during pregnancy reduces blood pressure in the mother and blood flow across the placenta.

Interactions

Like organic nitrates, amyl nitrite and other inhaled volatile nitrites may potentiate the hypotensive effects of phosphodiesterase type-5 inhibitors, see Interactions, under Sildenafil, p. 2366.3.

Pharmacokinetics

Amyl nitrite is absorbed via the skin, lungs, mucous membranes, and the gastrointestinal tract. Therapeutic effects are seen within 1 minute of inhalation. It is metabolised rapidly in the liver by hydrolytic denitration and excreted as both metabolites and unchanged drug in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *S.Afr.*: Tripac-Cyano; *USA*: Cyanide Antidote Package: Emergent-Ez.

Homoeopathic Preparations. *Austral.*: Hot Flush & Menopause Relief; Hot Flush & Menopause Relief; *Canad.*: Menopause.

Pharmacopoeial Preparations
USP 36: Amyl Nitrite Inhalant.

Asoxime Chloride

Asoxima, cloruro de; Chlorek Azoksymu; HI-6.
1-{[4-(Aminocarbonyl)pyridinio]methoxy}methyl)-2-[(hydroxyimino)methyl]pyridinium dichloride.
$C_{14}H_{16}Cl_2N_4O_3$=359.2
CAS — 34433-31-3.
UNII — HUV88P6SJS.

Profile

Asoxime chloride is a cholinesterase reactivator that has been tried in the treatment of poisoning by organophosphorus pesticides and related compounds, including nerve agents.

References.
1. Jovanović D, *et al.* A case of unusual suicidal poisoning by the organophosphorus insecticide dimethoate. *Hum Exp Toxicol* 1990; 9: 49–51.
2. Kušić R, *et al.* HI-6 in man: efficacy of the oxime in poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 1991; 10: 113–18.
3. Lundy PM, *et al.* Development of the bisquaternary oxime HI-6 toward clinical use in the treatment of organophosphate nerve agent poisoning. *Toxicol Rev* 2006; 25: 231–43.

AST-120

CAS — 90597-58-3.

Profile

AST-120 is a form of activated charcoal (p. 1537.3) consisting of spherical microcrystalline carbonaceous particles with oxygen complex including surface oxides. It is given orally as an adsorbent to delay the progression of chronic renal failure by removing uraemic toxins and their precursors from the gastrointestinal tract. It is also under investigation in hepatic encephalopathy and gastrointestinal disorders.

References.
1. Takahashi N, *et al.* Therapeutic effects of long-term administration of an oral adsorbent in patients with chronic renal failure: two-year study. *Int J Urol* 2005; 12: 7–11.
2. Ueda H, *et al.* AST-120, an oral adsorbent, delays the initiation of dialysis in patients with chronic kidney diseases. *Ther Apher Dial* 2007; 11: 189–95.
3. Fukuda Y, *et al.* Oral spherical adsorptive carbon for the treatment of intractable anal fistulas in Crohn's disease: a multicenter, randomized, double-blind, placebo-controlled trial. *Am J Gastroenterol* 2008; 103: 1721–9.
4. Shen B, *et al.* The efficacy and tolerability of AST-120 (spherical carbon adsorbent) in active pouchitis. *Am J Gastroenterol* 2009; 104: 1468–74.
5. Akizawa T, *et al.* CAP-KD Study Group. Effect of a carbonaceous oral adsorbent on the progression of CKD: a multicenter, randomized, controlled trial. *Am J Kidney Dis* 2009; 54: 459–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Kremezin; Kyucal.

Atipamezole *(BAN, USAN, rINN)*

Atipamezol; Atipamézole; Atipamezolum; MPV-1248; Атипамезол.
4-(2-Ethyl-2-indanyl)imidazole.
$C_{14}H_{16}N_2$=212.3
CAS — 104054-27-5.
ATC Vet — QV03AB90.
UNII — 03N9U5JAF6.

Atipamezole Hydrochloride *(BANM, rINNM)*

Atipametsolihydrokloridi; Atipamezol, hidrocloruro de; Atipamézole, Chlorhydrate d'; Atipamezolhydroklorid; Atipamezoli Hydrochloridum; Hidrocloruro de atipamezol; Атипамезола Гидрохлорид.
$C_{14}H_{16}N_2$,HCl=248.8
CAS — 104075-48-1.
UNII — 2W4279571X.

Profile

Atipamezole is a selective alpha$_2$-adrenergic receptor antagonist that is used as the hydrochloride in veterinary medicine to reverse the sedative effects of medetomidine.

References.
1. Pertovaara A, *et al.* Pharmacological properties, central nervous system effects, and potential therapeutic applications of atipamezole, a selective alpha2-adrenoceptor antagonist. *CNS Drug Rev* 2005; 11: 273–88.

Bixalomer *(USAN, rINN)*

AMG-223; ASP-1585; Bixalomère; Bixalómero; Bixalomerum; Биксаломер.
N,N,N',N'-Tetrakis(3-aminopropyl)butane-1,4-diamine polymer with 2-(chloromethyl)oxirane.
$(C_{18}H_{40}N_6)_n(C_3H_5ClO)_y$
CAS — 851373-13-2.
UNII — 3160WY51LV.

Profile

Bixalomer is a phosphate binder used for hyperphosphataemia (p. 1776.3) in patients with chronic renal failure. It is given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Kiklin.

Calcium Polystyrene Sulfonate

Calcium Polystyrene Sulphonate; Poliestirenosulfonato cálcico; Polistiren Sülfonat Kalsiyum; Полистирен Сульфонат Кальция.
CAS — 37286-92-3.
ATC — V03AE01.
ATC Vet — QV03AE01.

Pharmacopoeias. In *Br.* and *Jpn.*

BP 2014: (Calcium Polystyrene Sulfonate). A cream to light brown, fine powder. The calcium content is not less than 6.5% and not more than 9.5%, calculated with reference to the dried substance. Each g exchanges not less than 1.3 mmol and not more than 2.0 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water and in alcohol. Store in airtight containers.

Uses and Administration

Calcium polystyrene sulfonate, the calcium salt of sulfonated styrene polymer, is a cation-exchange resin that exchanges calcium ions for potassium ions and other cations in the gastrointestinal tract. It is used similarly to sodium polystyrene sulfonate (p. 1575.2) to enhance potassium excretion in the treatment of hyperkalaemia (p. 1777.1) associated with anuria or severe oliguria, and in dialysis patients. It may be preferred to the sodium resin in patients who cannot tolerate an increase in their sodium load. It is estimated that 1 g of calcium polystyrene sulfonate could bind 1.3 to 2 mmol of potassium but it is unlikely that such figures could be achieved in practice.

It is given orally or via a nasogastric tube in a usual dose of 15 g three or four times daily, as a suspension in water or syrup or as a sweetened paste. About 3 to 4 mL of vehicle has been suggested for each gram of resin. It should not be given in fruit juices that have a high potassium content.

When oral administration is difficult, calcium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 150 mL of water or glucose 10%, or 100 mL of 2% methylcellulose plus 100 mL of water, and retained, if possible, for at least 9 hours. Initial therapy may involve both oral and rectal routes. Following retention of the enema the colon should be irrigated to remove the resin.

For doses in children, see below.

Administration in children. Calcium polystyrene sulfonate is used in neonates and children to enhance potassium excretion in the treatment of hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients. Use is not recommended in neonates with reduced gut motility. It may be given orally as a suspension or paste, or rectally; calcium polystyrene sulfonate to be given rectally is mixed with water or glucose 5 or 10%, diluted in the same ratio as that for adults, see above. Care is needed with rectal use in children as excessive dosage or inadequate dilution can result in impaction of the resin; however, the oral route is not recommended in neonates. Licensed product information recommends a dose of 1 g/kg daily in divided doses, reduced to a maintenance dose of 500 mg/kg daily in divided doses. The *BNFC* suggests the same doses (to a daily maximum of 60 g orally, or 30 to 40 g rectally).

Adverse Effects and Precautions

As for Sodium Polystyrene Sulfonate, p. 1575.3. Sodium overloading is not a problem with calcium polystyrene sulfonate, but calcium overloading and hypercalcaemia may occur. It should therefore be avoided in patients with conditions such as hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma. Patients should be monitored for electrolyte disturbances, especially hypokalaemia and hypercalcaemia.

Effects on the gastrointestinal tract. Intestinal necrosis has been reported after oral use of calcium polystyrene sulfonate in a patient with acute colonic pseudo-obstruction,[1] and after oral and rectal use in a uraemic patient;[2] neither patient was given sorbitol.

1. Goutorbe P, *et al.* Intestinal necrosis associated with orally administered calcium polystyrene sulfonate without sorbitol. *Ann Pharmacother* 2011; 45: 278.
2. Joo M, *et al.* Colonic mucosal necrosis following administration of calcium polystyrene [sic] sulfonate (Kalimate) in a uremic patient. *J Korean Med Sci* 2009; 24: 1207–11.

Effects on the lungs. An elderly man who died from cardiac arrest was found at autopsy to have bronchopneumonia associated with inhalation of calcium polystyrene sulfonate;[1] the resin had been given orally to treat hyperkalaemia.

1. Chaplin AJ, Millard PR. Calcium polystyrene sulphonate: an unusual cause of inhalation pneumonia. *BMJ* 1975; 3: 77–8.

Interactions

As for Sodium Polystyrene Sulfonate, p. 1576.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Resincalcio; RIC Calcio; *Austral.*: Calcium Resonium; *Austria*: CPS Pulver; Sorbisterit; *Belg.*: Kayexalate; Sorbisterit; *Braz.*: Sorcal; *Canad.*: Resonium Calcium; *Chile*: Sorbisterit; *China*: Calcium Resonium (鉀利生); *Cz.*: Calcium Resonium; Resical; *Denm.*: Resonium Calcium; Sorbisterit; *Fin.*: Sorbisterit; *Fr.*: Calcium-Sorbisterit†; Resikali; *Ger.*: Calcium Resonium†; CPS Pulver; Elutit-Calcium; Sorbisterit; *Gr.*: Calcium Resonium; *Hong Kong*: Calcium Resonium; *India*: Calcium Resonium; K-Bind; Kapstat; *Indon.*: Kalitake; *Irl.*: Calcium Resonium; Sorbisterit†; *Jpn*: Kalimate; *Malaysia*: Kalimate; *Neth.*: Sorbisterit; *Norw.*: Resonium Calcium; *NZ*: Calcium Resonium; *Philipp.*: Kalimate; *Pol.*: Calcium Resonium; *Port.*: Resical; *Spain*: Resincalcio; Sorbisterit; *Swed.*: Resonium Calcium; Sorbisterit; *Switz.*: Sorbisterit; *Thai.*: Kalimate; Resincalcio; *Turk.*: Anti-putasium; *UK*: Calcium Resonium; Sorbisterit.

Deferasirox *(USAN, rINN)*

CGP-72670; Deferasiroks; Deferasirox; Deferasiroxum; ICL-670; ICL-670A; Деферазирокс.
4-[3,5-Bis(2-hydroxyphenyl)-1*H*-1,2,4-triazol-1-yl]benzoic acid.
$C_{21}H_{15}N_3O_4$=373.4
CAS — 201530-41-8.
ATC — V03AC03.
ATC Vet — QV03AC03.
UNII — V8G4MOF2V9.

Uses and Administration

Deferasirox is an orally active selective iron chelator that is used in the management of chronic iron overload (p. 1545.2) due to blood transfusion or non-transfusion dependent thalassaemia syndromes. Two moles of deferasirox bind with one mole of ferric ion to form a water-soluble iron complex; theoretically 100 mg of deferasirox can bind about 7.5 mg of iron, but in practice oral doses of 20 mg/kg daily are thought to result in iron losses of about 330 micrograms/kg each day. Deferasirox is available as tablets that may be dispersed in water, orange juice, or apple juice immediately before use. It should be taken on an empty stomach at least 30 minutes before food.

The usual initial dose for transfusional iron overload is 20 mg/kg once daily. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary, in steps of 5 to 10 mg/kg. Treatment should be withheld if serum-ferritin concentrations consistently fall below 500 micrograms/litre. Doses above 40 mg/kg daily are not recommended.

In iron overload of non-transfusion dependent thalassaemia syndromes, the usual initial dose is 10 mg/kg once daily. If the baseline liver-iron concentration is more than 15 mg of iron per gram of liver dry weight, the dose may be increased to 20 mg/kg daily after 4 weeks. Serum ferritin should be monitored monthly and the dose should be adjusted every 3 to 6 months as necessary, in steps of 5 to 10 mg/kg. Doses above 20 mg/kg daily (10 mg/kg daily in children) are not recommended. Treatment should be stopped when a satisfactory body-iron level has been achieved (serum-ferritin concentration below 300 micrograms/litre or liver-iron concentration below 3 mg of iron per gram of liver dry weight).

When deferasirox needs to be used with potent uridine diphosphate glucuronosyltransferase (UGT) inducers such as carbamazepine, rifampicin, phenytoin, phenobarbital, and ritonavir, or with colestyramine, the initial dose may be increased by 50% and adjusted according to serum-ferritin concentrations and response. For doses in children and in those with hepatic or renal impairment, see below.

References.

1. VanOrden HE, Hagemann TM. Deferasirox—an oral agent for chronic iron overload. *Ann Pharmacother* 2006; **40**: 1110–17.
2. Stumpf JL. Deferasirox. *Am J Health-Syst Pharm* 2007; **64**: 606–16.
3. Yang LPH, *et al.* Deferasirox: a review of its use in the management of transfusional chronic iron overload. *Drugs* 2007; **67**: 2211–30.
4. Vichinsky E. Clinical application of deferasirox: practical patient management. *Am J Hematol* 2008; **83**: 398–402.
5. Cappellini MD, Taher A. Long-term experience with deferasirox (ICL670), a once-daily oral iron chelator, in the treatment of transfusional iron overload. *Expert Opin Pharmacother* 2008; **9**: 2391–2402.
6. McLeod C, *et al.* Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation. *Health Technol Assess* 2009; **13**: 1–121.
7. Jabbour E, *et al.* Managing iron overload in patients with myelodysplastic syndromes with oral deferasirox therapy. *Oncologist* 2009; **14**: 489–96.
8. Kontoghiorghes GJ. Introduction of higher doses of deferasirox: better efficacy but not effective iron removal from the heart and increased risks of serious toxicities. *Expert Opin Drug Safety* 2010; **9**: 633–41.
9. Meerpohl JJ, *et al.* Deferasirox for managing transfusional iron overload in people with sickle cell disease. Available in The Cochrane Database of Systematic Reviews; Issue 8. Chichester: John Wiley; 2010 (accessed 12/11/10).
10. Ladis V, *et al.* Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia. *Br J Haematol* 2010; **151**: 504–8. Correction. *ibid.*; **152**: 124.
11. Vichinsky E, *et al.* Long-term safety and efficacy of deferasirox (Exjade) for up to 5 years in transfusional iron-overloaded patients with sickle cell disease. *Br J Haematol* 2011; **154**: 387–97.
12. Cappellini MD, *et al.* Iron chelation with deferasirox in adult and pediatric patients with thalassemia major: efficacy and safety during 5 years' follow-up. *Blood* 2011; **118**: 884–93.
13. Taher AT, *et al.* Deferasirox reduces iron overload significantly in nontransfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study. *Blood* 2012; **120**: 970–7.

Administration in children. Deferasirox is used for the management of chronic iron overload due to blood transfusion in children from 2 years of age, and for overload due to non-transfusion dependent thalassaemia syndromes in patients aged 10 years and older. It can generally be given in adult doses, see above. For dose adjustments in renal impairment, see below.

Administration in hepatic impairment. Deferasirox is not recommended in those with severe hepatic impairment (Child-Pugh class C). Those with mild or moderate (Child-Pugh class A or B, respectively) hepatic impairment should be monitored closely and the dose titrated as necessary. US licensed product information recommends that patients with moderate impairment be given 50% of the suggested starting dose (see Uses and Administration above). In the UK product information it is recommended that, in patients with moderate hepatic impairment, the deferasirox dose is considerably reduced, followed by progressive increases up to a maximum of 50% of the suggested starting dose.

Deferasirox therapy should be interrupted and/or the dose reduced if severe or persistent increases in liver enzymes or bilirubin occur during treatment.

Administration in renal impairment. Deferasirox doses should be adjusted in renal impairment (for monitoring requirements, see Adverse Effects and Precautions, below). Licensed product information varies between countries but recommended indicators for dose adjustment include a fall in estimated creatinine clearance (CC) to below 90 mL/minute, an increase in serum-creatinine concentration of more than 33% above average pretreatment values, and, particularly in children, a rise of serum-creatinine concentration above the age-appropriate upper limit of normal.

In patients being treated for chronic iron overload due to blood transfusion, the daily dose should be reduced by 10 mg/kg. If renal function deteriorates further then treatment with deferasirox should be stopped. Treatment may be restarted if individual circumstances allow. In patients being treated for non-transfusion dependent thalassaemia syndromes, adult doses should be reduced by 50% or stopped if the dose is 5 mg/kg daily; in children the dose may be reduced by 5 mg/kg.

In the USA, deferasirox is contra-indicated in patients with a CC of less than 40 mL/minute or a serum creatinine more than twice the age-appropriate upper limit of normal, whereas in the UK it is contra-indicated in those with an estimated CC of less than 60 mL/minute.

Mucormycosis. Deferasirox has been used successfully as an adjunct to antifungal therapy in the treatment of mucormycosis (p. 566.3),[1-3] although some treatment failures have also been reported.[2,4] Oral doses of about 15 to 20 mg/kg daily have been used,[1,2] usually with liposomal amphotericin B with which it is reported to be synergistic.[3] Deferasirox starves mucormycetes of the iron required for growth, unlike desferrioxamine which enhances iron uptake by the fungus (see p. 1547.2). Deferasirox may also enhance the inflammatory response to the infection.[4]

1. Reed C, *et al.* Deferasirox, an iron-chelating agent, as salvage therapy for rhinocerebral mucormycosis. *Antimicrob Agents Chemother* 2006; **50**: 3968–9.
2. Spellberg B, *et al.* Safety and outcomes of open-label deferasirox iron chelation therapy for mucormycosis. *Antimicrob Agents Chemother* 2009; **53**: 3122–5.
3. Busca A, *et al.* Combined antifungal therapy, iron chelation and surgical resection as treatment of hepatic zygomycosis in a patient with haematological malignancy. *Mycoses* 2010; **53**: 275–6.
4. Soummer A, *et al.* Failure of deferasirox, an iron chelator agent, combined with antifungals in a case of severe zygomycosis. *Antimicrob Agents Chemother* 2008; **52**: 1585–6.

Adverse Effects and Precautions

The commonest adverse effects with deferasirox are dose-related gastrointestinal disorders, such as nausea, vomiting, diarrhoea, and abdominal pain; diarrhoea may be more common in young children and the elderly. Upper gastrointestinal ulceration and haemorrhage, sometimes fatal, have been reported; fatal haemorrhages were more common in elderly patients with advanced malignancies and/or low platelet counts. Rashes are common and may respond to a reduction in dose; erythema multiforme has been reported. Serious hypersensitivity reactions such as anaphylaxis and angioedema have been reported, usually within the first month of deferasirox treatment. Other adverse effects include headache, pyrexia, pruritus, anxiety, sleep disorders, fatigue, dizziness, skin pigmentation disorders, infections, pharyngolaryngeal pain, and oedema. Leucocytoclastic vasculitis, urticaria, and alopecia have occurred.

Dose-dependent increases in serum creatinine are common and proteinuria may also occur. There have been reports of acute renal failure, including fatalities; renal tubulopathy, has occurred, mainly in children and adolescents with β-thalassaemia.

US licensed product information recommends that renal function is measured before starting therapy, and at least monthly thereafter. In high-risk patients, such as those with pre-existing renal impairment or at increased risk of acute renal failure, renal function should be measured weekly during the first month of treatment or after adjusting the dose, and monthly thereafter. Deferasirox should not be used in patients with a CC below 40 mL/minute or with a serum-creatinine more than twice the upper limit of normal.

In the UK, where deferasirox is not recommended in those with a CC below 60 mL/minute, all patients should have their renal function measured at baseline, weekly during the first month of treatment or after adjusting the dose, and monthly thereafter.

Tests for proteinuria should also be performed monthly. The dose should be reduced or treatment stopped if persistent increases in serum creatinine occur, see Administration in Renal Impairment, above.

Liver enzyme values may increase in patients receiving deferasirox, and cases of hepatitis and hepatic failure, sometimes fatal, have occurred. Gallstones have also been reported. Liver enzymes and bilirubin should be measured before starting deferasirox, every 2 weeks during the first month, and monthly thereafter. The dose of deferasirox may need to be modified in those with pre-existing hepatic impairment, or if increases in liver enzymes or bilirubin occur during treatment, see Administration in Hepatic Impairment, above.

As with other iron chelators, hearing loss and visual disorders, including cataracts, have occurred. Audiological and ophthalmological tests should be performed before starting deferasirox and then every 12 months. In children, annual assessment of growth and development is also recommended.

Serum ferritin should be measured monthly to assess patient response and avoid overchelation of iron. Treatment should be withheld if the value is consistently below 500 micrograms/litre in patients being treated for transfusional iron overload, or below 300 micrograms/litre in those with non-transfusion dependent thalassaemia syndromes.

There have been rare reports of blood disorders, some of which have been fatal, including agranulocytosis, neutropenia, and thrombocytopenia, in patients taking deferasirox. Blood counts should be monitored regularly. Deferasirox should be used with caution, if at all, when platelet counts are less than 50 000 cells/mm^3.

Serious adverse effects, including fatalities, were more often reported in elderly patients, in those with comorbidities such as pre-existing renal or hepatic impairment, or in those with advanced disease; deferasirox is therefore contra-indicated in those with a poor performance status, high-risk myelodysplastic syndromes, or advanced malignancies.

Hyperferritinaemia. Although serum-ferritin concentrations are generally considered to be a proxy measure for iron overload in patients with thalassaemia, there has been a report[1] of a patient in whom switching from desferrioxamine to oral deferasirox chelation therapy was associated with progressive rises in serum ferritin which were not paralleled by increases in body-iron as measured by MRI. After six months of therapy with deferasirox, serum ferritin had increased from about 600 to over 2700 ng/mL, despite progressive increases in deferasirox dosage from 10 to 30 mg/kg daily. On stopping the drug and resuming desferrioxamine the ferritin values returned to baseline.

1. Ricchi P, *et al.* Paradoxically increased ferritin level in a beta-thalassemia major patient following the start of deferasirox chelation therapy. *Acta Haematol (Basel)* 2010; **123**: 117–20.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies deferasirox as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. A report[1] of a successful birth after use of deferasirox during pregnancy.

1. Ricchi P, *et al.* A case of well-tolerated and safe deferasirox administration during the first trimester of a spontaneous pregnancy in an advanced maternal age thalassemic patient. *Acta Haematol (Basel)* 2011; **125**: 222–224.

Interactions

Deferasirox should not be given with aluminium-containing antacids since there is a possibility that it may chelate aluminium. The metabolism of deferasirox depends on uridine diphosphate glucuronosyltransferase (UGT) enzymes, and use with potent inducers of these enzymes such as carbamazepine, rifampicin, phenytoin, phenobarbital, and ritonavir may decrease exposure to deferasirox. The dose of deferasirox may need to be increased and the serum ferritin monitored (see also Uses and Administration, above).

Exposure to deferasirox was reduced when it was given with colestyramine, and their use together should be avoided. An increased initial dose of deferasirox should be considered if treatment with both drugs is necessary (see Uses and Administration, above).

Deferasirox inhibits cytochrome P450 isoenzymes CYP1A2 and CYP2C8, and may induce CYP3A4. Caution is advised when deferasirox is given with drugs which are metabolised by these isoenzymes.

References.

1. Skerjanec A, *et al.* Investigation of the pharmacokinetic interactions of deferasirox, a once-daily oral iron chelator, with midazolam, rifampin, and repaglinide in healthy volunteers. *J Clin Pharmacol* 2010; **50**: 205–13.

Pharmacokinetics

Deferasirox is absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1.5 to 4 hours after ingestion. The absolute bioavailability is about 70% but is increased in the presence of food. Deferasirox is about 99% bound to plasma proteins, mainly albumin. Metabolism of deferasirox is mainly glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes. Cytochrome P450 isoenzyme-mediated metabolism appears to be minor. Deconjugation of the glucuronidates in the intestine and subsequent enterohepatic recycling are likely to occur. It is excreted mainly in the faeces via bile, as metabolites and as unchanged drug. About 8% of a dose is excreted in the urine. The mean elimination half-life is about 8 to 16 hours.

Children and adolescents have a lower exposure to deferasirox than adults; in children under 6 years of age exposure was about 50% lower. Men have a higher clearance of deferasirox than women.

References.
1. Galanello R, *et al.* Effect of food, type of food, and time of food intake on deferasirox bioavailability: recommendations for an optimal deferasirox administration regimen. *J Clin Pharmacol* 2008; **48**: 428–35.
2. Séchaud R, *et al.* Absolute oral bioavailability and disposition of deferasirox in healthy human subjects. *J Clin Pharmacol* 2008; **48**: 919–25.
3. Chirnomas D, *et al.* Deferasirox pharmacokinetics in patients with adequate versus inadequate response. *Blood* 2009; **114**: 4009–13.
4. Waldmeier F, *et al.* Pharmacokinetics, metabolism, and disposition of deferasirox in beta-thalassemic patients with transfusion-dependent iron overload who are at pharmacokinetic steady state. *Drug Metab Dispos* 2010; **38**: 808–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Exjade; ***Austral.***: Exjade; ***Austria***: Exjade; ***Belg.***: Exjade; ***Braz.***: Exjade; ***Canad.***: Exjade; ***Chile***: Exjade; ***China***: Exjade (恩瑞格); ***Cz.***: Exjade; ***Denm.***: Exjade; ***Fr.***: Exjade; ***Ger.***: Exjade; ***Gr.***: Exjade; ***Hong Kong***: Exjade; ***Hung.***: Exjade; ***Indon.***: Exjade; ***Irl.***: Exjade; ***Israel***: Exjade; ***Ital.***: Exjade; ***Malaysia***: Exjade; ***Neth.***: Exjade; ***Norw.***: Exjade; ***NZ***: Exjade; ***Philipp.***: Exjade; ***Pol.***: Exjade; ***Port.***: Exjade; ***Rus.***: Exjade (Эксиджад); ***S.Afr.***: Exjade; ***Singapore***: Exjade; ***Spain***: Exjade; ***Swed.***: Exjade; ***Switz.***: Exjade; ***Thai.***: Exjade; ***Turk.***: Exjade; ***UK***: Exjade; ***Ukr.***: Exjade (Эксиджад); ***USA***: Exjade.

Deferiprone *(BAN, USAN, rINN)*

APO-066; APO-66; CP-20; Deferipron; Deferiprona; Déferiprone; Deferiproni; Deferipronum; Deferypron; Dimethylhydroxypyridone; DN-180-01-AF; L-1; L1; PL-1; Деферипрон.

1,2-Dimethyl-3-hydroxypyrid-4-one; 3-Hydroxy-1,2-dimethyl-4-pyridone.

$C_7H_9NO_2$=139.2

CAS — 30652-11-0.

ATC — V03AC02.

ATC Vet — QV03AC02.

UNII — 2BTY8KH53L

Uses and Administration

Deferiprone is an orally active iron chelator used in the treatment of iron overload in patients with thalassaemia for whom desferrioxamine is unsuitable or ineffective. Three moles of deferiprone bind with one mole of ferric ion to form a stable water-soluble iron complex; theoretically 100 mg of deferiprone can bind about 13.4 mg of iron, but as with other iron chelators, it is unlikely that such a figure could be achieved in practice. Deferiprone may be given in oral doses of 25 mg/kg three times daily. Doses above 100 mg/kg daily are not recommended. For use in children, see Administration in Children, below.

Reviews.
1. Hoffbrand AV. Deferiprone therapy for transfusional iron overload. *Best Pract Res Clin Haematol* 2005; **18**: 299–317.
2. Piga A, *et al.* Deferiprone: new insight. *Ann N Y Acad Sci* 2005; **1054**: 169–74.
3. Kattamis A. Combined therapy with deferoxamine and deferiprone. *Ann N Y Acad Sci* 2005; **1054**: 175–82.
4. Roberts D, *et al.* Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 29/07/10).
5. Galanello R, Campus S. Deferiprone chelation therapy for thalassemia major. *Acta Haematol (Basel)* 2009; **122**: 155–64.
6. Cappellini MD, *et al.* Overview of iron chelation therapy with desferrioxamine and deferiprone. *Hemoglobin* 2009; **33** (suppl 1): S58–S69.

Administration in children. UK licensed product information states that there are limited data on the use of deferiprone in children between 6 and 10 years of age, and no data on use in children below 6. Australian licensed product information states that limited data exist for children between the ages of 2 and 10 but that the effects of deferiprone on growth are unknown. Licensed doses in children are calculated by weight on the same basis as adults (see Uses and Administration, above).

A study evaluating an oral liquid formulation in 100 children aged between 1 and 10 years with transfusion-dependent anaemia found that an oral dose of deferiprone 50 to 100 mg/kg daily in three divided doses reduced serum-ferritin concentrations. Adverse effects were similar to those reported in adults, although an increase in serum-creatinine concentration was seen in 2 children during treatment, which resolved at the end of the 6-month study.[1]

In a retrospective study in 17 paediatric haematology or oncology patients with iron overload, rather lower doses of 20 to 40 mg/kg [daily] as tablets were found to be effective.[2]

1. El Alfy M, *et al.* The safety, tolerability, and efficacy of a liquid formulation of deferiprone in young children with transfusional iron overload. *J Pediatr Hematol Oncol* 2010; **32**: 601–5.
2. Won SC, *et al.* Efficacy and safety of deferiprone (Ferriprox), an oral iron-chelating agent, in pediatric patients. *Korean J Hematol* 2010; **45**: 58–61.

Iron distribution. Deferiprone has been investigated as a therapeutic strategy for relocating iron in disorders with defective iron distribution such as anaemia of chronic disease, or the neurodegenerative disorders Friedreich's ataxia, Alzheimer's disease, or Parkinson's disease.[1,2]

1. Kakhlon O, *et al.* Iron redistribution as a therapeutic strategy for treating diseases of localized iron accumulation. *Can J Physiol Pharmacol* 2010; **88**: 187–96.
2. Kakhlon O, *et al.* Cell functions impaired by frataxin deficiency are restored by drug-mediated iron relocation. *Blood* 2008; **112**: 5219–27.

Malaria. Deferiprone has been investigated for the treatment of malaria, see Malaria, under Desferrioxamine, p. 1546.1.

Thalassaemia. Patients with thalassaemia receiving regular blood transfusions commonly develop iron overload requiring use of iron chelators. Deferiprone was developed as an oral alternative to desferrioxamine, but its role has been controversial. See Thalassaemia under Uses of Desferrioxamine, p. 1545.2, for further information.

Adverse Effects, Treatment, and Precautions

Deferiprone commonly causes neutropenia, agranulocytosis, and thrombocytopenia and should not be used in neutropenic patients or in those with a history of agranulocytosis or recurrent neutropenia. The neutrophil count should be monitored weekly and treatment permanently stopped if neutropenia develops. Supportive treatment such as granulocyte colony-stimulating factor is recommended in those with severe neutropenia. Patients should be advised to seek immediate medical attention if symptoms indicative of infection such as fever, sore throat, or flu-like symptoms occur. Deferiprone should be withheld if an infection develops and the neutrophil count monitored more frequently.

Gastrointestinal disorders such as diarrhoea, nausea, vomiting, and abdominal pain are common during initial treatment with deferiprone. Most cases resolve with continued treatment, but some may require a temporary reduction in dose. A reddish-brown discoloration of the urine commonly occurs due to excretion of the iron-deferiprone complex. Other common adverse effects include headache, an increase or decrease in appetite, asthenia, musculoskeletal pain, peripheral oedema, dizziness, somnolence, pruritus, and urticaria. Arthropathy also occurs and can range from mild arthralgia to severe arthritis.

Serum ferritin should be measured every 2 or 3 months; treatment may need to be withheld if concentrations fall below 500 micrograms/litre. Deferiprone may reduce plasma-zinc concentrations and these should also be monitored and zinc supplements started if required.

Deferiprone is teratogenic in *animals* and should not be used during pregnancy. Women of child-bearing potential should be advised to use contraceptive measures during treatment with deferiprone.

Caution is advised in patients with hepatic or renal impairment and organ function should be monitored during therapy. Increased serum concentrations of alanine aminotransferase (ALT) have occurred; therapy may be withheld for persistent increases in ALT. For mention of an increase in serum-creatinine concentrations in some children treated with deferiprone, see Administration in Children, above.

A total daily dose above 100 mg/kg is not recommended due to the potential increased risk of adverse effects. Neurological disorders have been reported in children treated with higher than recommended doses of deferiprone, see Overdosage, below.

Auto-immune disorders. Deferiprone has been associated with isolated reports of auto-immune disorders such as Henoch-Schönlein purpura,[1] systemic vasculitis,[2] and a fatal case of SLE;[3] arthritic reactions are common. Although some thalassaemia patients treated with deferiprone had small increases in autoantibodies associated with SLE, no other symptoms were seen. Monitoring for autoantibodies and other immune abnormalities has been suggested.[4]

1. Unal S, *et al.* Severe Henoch-Schönlein purpura in a thalassemic patient under deferiprone treatment. *Am J Hematol* 2008; **83**: 165–6.
2. Castriota-Scanderbeg A, Sacco M. Agranulocytosis, arthritis and systemic vasculitis in a patient receiving the oral iron chelator L1 (deferiprone). *Br J Haematol* 1997; **96**: 254–5.
3. Mehta J, *et al.* Fatal systemic lupus erythematosus in patient taking oral iron chelator L1. *Lancet* 1991; **337**: 298.
4. Mehta J, *et al.* Oral iron chelator L1 and autoimmunity. *Blood* 1993; **81**: 1970–2.

Effects on the blood. Agranulocytosis, in some cases fatal, has been associated with deferiprone use.[1-3]

1. Henter J-I, Karlén J. Fatal agranulocytosis after deferiprone therapy in a child with Diamond-Blackfan anemia. *Blood* 2007; **109**: 5157–9.
2. Tewari S, *et al.* Necrotizing stomatitis: a possible periodontal manifestation of deferiprone-induced agranulocytosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; **108**: e13–e19.
3. Pontikoglou C, Papadaki HA. Idiosyncratic drug-induced agranulocytosis: the paradigm of deferiprone. *Hemoglobin* 2010; **34**: 291–304.

Effects on the ears and eyes. Like other iron chelators, adverse effects on the ears and eyes have been reported with deferiprone, including subclinical auditory and visual impairment,[1] and a higher incidence of retinal pigment epithelial degeneration.[2] In 2 reported cases of posterior subcapsular opacity the opacities were associated with red-dish-brown deposits suggestive of iron accumulation.[3]

Hearing loss associated with desferrioxamine therapy remained stable or worsened when treatment was changed to deferiprone in 5 of 16 adults, although it was unclear if this reflected progression or irreversibility of the desferrioxamine damage or if deferiprone caused additional ototoxicity.[4]

1. Marciani MG, *et al.* Subclinical auditory and visual involvement during oral deferiprone therapy. *Am J Hematol* 1996; **51**: 179–80.
2. Taneja R, *et al.* Multiple transfused thalassemia major: ocular manifestations in a hospital-based population. *Indian J Ophthalmol* 2010; **58**: 125–30.
3. Mehdizadeh M, Nowroozzadeh MH. Posterior subcapsular opacity in two patients with thalassaemia major following deferiprone consumption. *Clin Exp Optom* 2009; **92**: 392–4.
4. Chiodo AA, *et al.* Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; **26**: 116–22.

Hepatic fibrosis. Hepatic fibrosis was reported to have progressed in 5 patients with thalassaemia treated with deferiprone,[1] although other studies have found no evidence to suggest that deferiprone exacerbated liver fibrosis.[2-4]

1. Olivieri NF, *et al.* Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; **339**: 417–23.
2. Wu S-P, *et al.* Liver fibrosis and iron levels during long-term deferiprone treatment of thalassemia major patients. *Hemoglobin* 2006; **30**: 215–18.
3. Chen A-C, *et al.* Effect of deferiprone on liver iron overload and fibrosis in hepatitis-C-virus-infected thalassemia. *Hemoglobin* 2006; **30**: 209–14.
4. Wanless IR, *et al.* Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood* 2002; **100**: 1566–9. Correction. *Ibid.* 2003; **101**: 2460.

Overdosage. Neurological disorders were reported by the manufacturer and the French pharmacovigilance authorities in 2 children aged 7 and 9 who had been treated with deferiprone doses at 2½ times the highest recommended dose of 100 mg/kg daily. The children were treated for 1 and 2 years, respectively, and developed nystagmus, gait disorders, ataxia, dystonia, and, in one case, psychomotor retardation. These disorders gradually improved after deferiprone was stopped.[1]

Cerebellar syndrome was also reported in 2 children given deferiprone at higher than recommended doses.[2] The first patient was treated for more than 3 years before developing dizziness, axial hypotonia, nystagmus, diplopia, and obsessive-compulsive disorder. The second developed impaired motor coordination, dystonia, nystagmus, and the inability to walk in a straight line after 2 months of high-dose treatment. Again, symptoms in both patients gradually improved once deferiprone was stopped.

1. Agence française de sécurité sanitaire des produits de santé/Laboratoires Chiesi, France. Risque d'agranulocytoses fatales et de troubles neurologiques lors de l'utilisation de Ferriprox(déféripirone) (issued 1st September, 2006). Available at: http://www.afssaps.fr/content/download/12879/156735/version/1/file/lp060901.pdf (accessed 12/08/10)
2. Beau-Salinas F, *et al.* High doses of deferiprone may be associated with cerebellar syndrome. *BMJ* 2009; **338**: a2319.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies deferiprone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Interactions

Deferiprone chelates trivalent metal ions and could interact with aluminium-containing preparations; it should not be given with aluminium-containing antacids. Due to the risk

of additive toxicity, use with drugs that may cause neutropenia or agranulocytosis is not recommended.

Pharmacokinetics

Deferiprone is rapidly absorbed from the gastrointestinal tract and peak serum concentrations occur 45 to 60 minutes after an oral dose; absorption may be slowed in the presence of food and peak serum concentrations may be reduced. Protein binding is low (less than 10%). Deferiprone is metabolised to an inactive glucuronide metabolite and is excreted mainly in the urine as the metabolite and the iron-deferiprone complex, with a small amount of unchanged drug. The elimination half-life is about 2 to 3 hours.

References.
1. Limenta LMG, *et al.* Pharmacokinetics of deferiprone in patients with β-thalassaemia: impact of splenectomy and iron status. *Clin Pharmacokinet* 2011; **50**: 41–50.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ferriprox; *Austral.*: Ferriprox; *Austria*: Ferriprox; *Belg.*: Ferriprox; *Braz.*: Ferriprox; *China*: Ferriprox (奥贝安可); *Cz.*: Ferriprox; *Denm.*: Ferriprox; *Fin.*: Ferriprox; *Fr.*: Ferriprox; *Ger.*: Ferriprox; *Gr.*: Ferriprox; Kelfer; *Hong Kong*: Ferriprox; *India*: Kelfer; *Indon.*: Ferriprox; *Irl.*: Ferriprox; *Israel*: Ferriprox; *Ital.*: Ferriprox; *Malaysia*: Ferriprox; Kelfer; *Neth.*: Ferriprox; *Norw.*: Ferriprox; *NZ*: Ferriprox; *Pol.*: Ferriprox; *Port.*: Ferriprox; *Singapore*: Ferriprox; Kelfer; *Spain*: Ferriprox; *Swed.*: Ferriprox; *Switz.*: Ferriprox; *Thai.*: Ferriprox; GPO-L-One; Kelfer; *Turk.*: Ferriprox; *UK*: Ferriprox; *USA*: Ferriprox.

Desferrioxamine Mesilate *(BANM)*

Ba-29837 (desferrioxamine hydrochloride); Ba-33112; Deferoksaminimesilaatti; Deferoksamin Mezilat; Deferoksamino mesilatas; Deferoxamina, mesilato de; Deferoxamine Mesilate (pINNM); Déferoxamine, Mésilate de; Déféroxamine, mésilate de; Deferoxamine Mesylate (USAN); Deferoxamini Mesilas; Deferoxaminmesilat; Deferoxamin-mesylát; Deferoxamin-mezilát; Desferrioksamin Mesilat; Desferrioxamine Mesylate; Desferrioxamine Methanesulphonate; Mesilato de deferoxamina; NSC-527604 (desferrioxamine); Дефероксамина Мезилат

30-Amino-3,14,25-trihydroxy-3,9,14,20,25-penta-azatriacontane-2,10,13,21,24-pentaone methanesulphonate; *N*'-[5-[(4-[[5-(Acetylhydroxyamino)pentyl]amino]-1,4-dioxobutyl) hydroxyamino]pentyl]-*N*-(5-aminopentyl)-*N*-hydroxy-butanediamide monomethanesulphonate.

$C_{25}H_{48}N_6O_8.CH_3SO_3H$=656.8

CAS — 70-51-9 (desferrioxamine); 138-14-7 (desferrioxamine mesilate); 1950-39-6 (desferrioxamine hydrochloride).

ATC — V03AC01.

ATC Vet — QV03AC01.

UNII — V9TKO7EO6K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Deferoxamine Mesilate; Desferrioxamine Mesilate BP 2014). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol; slightly soluble in methyl alcohol. A freshly prepared 10% solution in water has a pH of 3.7 to 5.5. Store at 2 degrees to 8 degrees. Protect from light.

USP 36: (Deferoxamine Mesylate). A white to off-white powder. Freely soluble in water; slightly soluble in methyl alcohol. pH of a 1% solution in water is between 4.0 and 6.0. Store in airtight containers.

Incompatibility. Licensed product information states that desferrioxamine solutions are incompatible with heparin.

Uses and Administration

Desferrioxamine is a chelator that has a high affinity for ferric iron. It appears to remove both free iron and iron bound to haemosiderin and ferritin but not iron bound to haemoglobin, transferrin, or cytochromes. One mole of desferrioxamine mesilate binds with one mole of ferric ion to form a stable complex, so theoretically 100 mg of desferrioxamine mesilate could bind about 8.5 mg of iron but it is unlikely that such a figure could be achieved in practice. Desferrioxamine also has an affinity for aluminium; one mole of desferrioxamine mesilate binds with one mole of aluminium to form a stable complex, so theoretically 100 mg of the mesilate could bind about 4.1 mg of aluminium.

Desferrioxamine increases the excretion of iron from the body and is used in the treatment of acute iron poisoning (see p. 1546.1) and for conditions associated with chronic iron overload; these include the treatment and diagnosis of the iron storage disorders haemochromatosis (when phlebotomy cannot be used) and haemosiderosis resulting from repeated blood transfusions as in thalassaemia. Desferrioxamine also increases the excretion of aluminium from the body and is used in the treatment and diagnosis of aluminium overload in patients with end-stage renal failure on maintenance dialysis. For further discussion of aluminium or iron overload, see below and p. 1545.2. Desferrioxamine is used in the diagnosis of some chronic anaemias such as sideroblastic anaemia (p. 1123.1) and auto-immune haemolytic anaemia (p. 1122.2).

Desferrioxamine is used as the mesilate and may be given by subcutaneous or intravenous infusion, by intramuscular injection, or intraperitoneally.

In the treatment of **acute iron poisoning**, desferrioxamine is usually given by intravenous infusion, particularly in patients who are symptomatic. However, US licensed product information advises intramuscular injection unless the patient is in shock, due to the risk of adverse effects with the intravenous route. The dose should be adjusted according to the severity of the poisoning, preferably as indicated by the serum-iron concentration and total iron binding capacity, if available, although chelation therapy should be started in patients with significant symptoms without waiting for the results of blood concentrations. In the UK, the usual initial dose of desferrioxamine mesilate is 15 mg/kg per hour by slow intravenous infusion, reducing after 4 to 6 hours to provide a total dose not exceeding 80 mg/kg in 24 hours, although larger doses may be tolerated. Alternatively, it may be given intramuscularly as a single dose of 2 g. In the USA, an initial dose of 1 g is given, either intravenously at a maximum rate of 15 mg/kg per hour, or by intramuscular injection. Subsequent doses of 500 mg may be given intravenously, at a rate not exceeding 125 mg/hour, or intramuscularly, every 4 hours for 2 doses, then every 4 to 12 hours according to response. A maximum dose of 6 g in 24 hours is recommended.

In the treatment of **chronic iron overload**, the dosage and route of administration should be determined for each patient by monitoring urinary iron excretion, with the aim of normalising serum-ferritin concentrations. Doses may be given by subcutaneous infusion, via an infusion pump, or by continuous intravenous infusion in those unable to have subcutaneous infusions or those with cardiac problems secondary to iron overload. An initial dose of 500 mg has been suggested, which may then be adjusted until a plateau of iron excretion is reached or with the aim of keeping the therapeutic index (the daily dose in mg/kg divided by the serum-ferritin concentration in micrograms/litre) below 0.025. The usual effective dose range is 20 to 60 mg/kg daily. Subcutaneous infusions are given 3 to 7 times a week depending on the degree of iron overload, usually over 8 to 12 hours, but infusion over 24 hours may be necessary in some patients. Although the UK considers subcutaneous infusion more effective, US licensed product information suggests an initial intramuscular dose of 0.5 to 1 g daily; a maximum dose of 1 g daily is recommended in the absence of a blood transfusion. Additional doses of desferrioxamine may be given at the time of blood transfusion; up to 2 g of desferrioxamine mesilate by intravenous infusion for each unit of blood transfused, at a rate of not more than 15 mg/kg per hour. Desferrioxamine should be given separately from the blood. In the USA the total dose from intramuscular injections plus intravenous infusions with blood transfusions should not exceed desferrioxamine mesilate 6 g daily. Ascorbic acid supplements (see Uses and Administration, under Vitamin C Substances, p. 2111.1) can enhance the excretion of iron, but, to reduce the risk of toxicity, should not be started until 1 month after starting desferrioxamine treatment (see under Interactions, p. 1547.3).

Desferrioxamine has been used as a *diagnostic test* for iron storage disease or some chronic anaemias in patients with normal renal function by injecting 500 mg of the mesilate intramuscularly and measuring the iron excreted in the urine over the next 6 hours. More than 1 mg of iron is suggestive of iron overload and more than 1.5 mg can be regarded as pathological.

In the treatment of **aluminium overload** in patients with end-stage renal failure, those undergoing maintenance haemodialysis or haemofiltration may be given desferrioxamine mesilate 5 mg/kg once a week by slow intravenous infusion during the last hour of a dialysis session, or 5 hours before dialysis in patients with more severe overload. Patients on peritoneal dialysis (CAPD or CCPD) may be given desferrioxamine mesilate 5 mg/kg once a week, by slow intravenous infusion, subcutaneously, intramuscularly, or intraperitoneally (the recommended route) before the final exchange of the day. For the *diagnosis* of aluminium overload, desferrioxamine mesilate 5 mg/kg is given by slow intravenous infusion during the last hour of haemodialysis. An increase in serum-aluminium concentration above baseline of more than 150 nanograms/mL (measured at the start of the next dialysis session) suggests aluminium overload.

For doses in children, see Administration in Children, below.

Administration. Compliance may be a problem with standard parenteral desferrioxamine regimens in patients with chronic iron overload. The oral,[1-3] rectal,[4] and intranasal[5] routes have therefore been tried as alternatives, but results have generally been disappointing. Twice-daily subcutaneous bolus injection has also been reported,[6-9] although the volume of the injection may be a limiting factor.[9]

Intraperitoneal desferrioxamine may be used to reduce aluminium levels in patients receiving peritoneal dialysis for chronic renal failure. Good results have also been reported[10] in a patient with haemochromatosis complicated by cirrhosis and cardiomyopathy, in whom a chronic peritoneal dialysis catheter was used to control ascites and to give desferrioxamine.

1. Callender ST, Weatherall DJ. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii**: 689.
2. Jacobs A, Chang Ting W. Iron chelation with oral desferrioxamine. *Lancet* 1980; **ii**: 794.
3. Kattamis C, *et al.* Oral desferrioxamine in young patients with thalassaemia. *Lancet* 1981; **i**: 51.
4. Kontoghiorghes G, *et al.* Desferrioxamine suppositories. *Lancet* 1983; **ii**: 454.
5. Gordon GS, *et al.* Intranasal administration of deferoxamine to iron overloaded patients. *Am J Med Sci* 1989; **297**: 280–4.
6. Borgna-Pignatti C, Cohen A. Evaluation of a new method of administration of the iron chelating agent deferoxamine. *J Pediatr* 1997; **130**: 86–8.
7. Franchini M, *et al.* Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload. *Blood* 2000; **95**: 2776–9.
8. Di Gregorio F, *et al.* An alternative to continuous subcutaneous infusion of desferrioxamine in thalassaemic patients. *Br J Haematol* 1997; **98**: 601–2.
9. Franchini M, *et al.* Safety and efficacy of subcutaneous bolus injection of deferoxamine in adult patients with iron overload: an update. *Blood* 2004; **103**: 747–8.
10. Swartz RD, Legault DJ. Long-term intraperitoneal deferoxamine for hemochromatosis. *Am J Med* 1996; **100**: 308–12.

Administration in children. Desferrioxamine is used in children to treat conditions associated with chronic iron overload (such as occurs in refractory anaemias as a result of repeated blood transfusions) and acute iron poisoning. It is also used to treat aluminium overload in children on dialysis.

For **acute iron poisoning** in children, desferrioxamine mesilate is usually given by continuous intravenous infusion in similar doses to those used in adults (see Uses and Administration, above). Alternatively, it may be given by intramuscular injection; UK licensed product information recommends a single dose of 1 g. In the USA, subsequent intramuscular dosage is suggested, as for adults.

For **chronic iron overload** in children, desferrioxamine mesilate is given to achieve iron balance and prevent haemosiderosis. The dosage should be determined by monitoring urinary iron excretion with the aim of normalising serum-ferritin concentrations. Doses are similar to those used in adults, although the *BNFC* suggests the initial dose should not exceed 30 mg/kg. In children under 3 years of age, the mean daily dose should not exceed 40 mg/kg to avoid growth retardation, see Precautions, p. 1546.2. Ascorbic acid (see p. 2111.2) can be given to enhance iron excretion.

Desferrioxamine mesilate is also given for **aluminium overload** in children on dialysis in the same dose as that used in adults.

Aluminium overload. Desferrioxamine is an effective aluminium chelator and may have a role in both acute and chronic aluminium toxicity. Accumulation of aluminium may be a particular problem in patients with chronic renal failure and has been implicated in renal osteodystrophy and dialysis dementia, as well as in other conditions, see Aluminium p. 2439.2. Acute aluminium toxicity is less common, but may occur following exposure to soluble aluminium salts.

Use of alternative phosphate binders (see Renal Osteodystrophy, p. 1170.1) and limits on the aluminium concentration of dialysis fluids reduce the exposure to aluminium in patients with chronic renal failure, but desferrioxamine may also be used to remove aluminium that has already accumulated. The desferrioxamine-aluminium chelate (aluminoxamine) is removed by haemoperfusion and by haemodialysis,[1] and also by peritoneal dialysis (although the amount removed may be much less), and desferrioxamine has been used successfully to treat aluminium overload in dialysis patients. It has also been used with dialysis in acute toxicity.

In patients with *dialysis encephalopathy*, increased aluminium excretion and clinical improvement has been reported[2,3] in patients given desferrioxamine in doses of up to 6 g once a week via the arterial line during the first 2 hours of haemodialysis.[2,3] A study[4] of 11 patients with dialysis encephalopathy found that 5 patients who were treated with deionised or reverse-osmosis water alone died, whereas of 6 who were also given desferrioxamine 6 to 10 g intravenously each week at dialysis, 4 showed clinical improvement. Substantial improvement in early aluminium encephalopathy has been achieved in a patient on

continuous ambulatory peritoneal dialysis by using intraperitoneal desferrioxamine.[5] Another small study[6] found that desferrioxamine improved psychomotor function in haemodialysis patients with impaired cerebral function but no clinical encephalopathy, who had only mildly elevated plasma-aluminium concentrations; desferrioxamine was given 3 times weekly during dialysis. Improvement in acute encephalopathy related to alum bladder irrigation has also been reported.[7] However, use of desferrioxamine may also exacerbate encephalopathy and caution is required (see Aluminium Encephalopathy, under Adverse Effects, Treatment, and Precautions, p. 1546.2).

Desferrioxamine has produced rapid clinical improvement in patients with *dialysis-related bone disease*.[8-10] In some studies[9,10] this has been associated with a reduction in the aluminium content of bone; others[8] have reported clinical improvement with no apparent effect on bone aluminium. Lower doses than those licensed for treatment (see Uses and Administration, p. 1544.1) have been evaluated; a once weekly intravenous dose of 2.5 mg/kg showed similar efficacy to the standard dose of 5 mg/kg in one study.[11] Diagnosis of aluminium-related bone disease may require bone biopsy, but some studies have suggested that measurement of plasma-aluminium concentrations after a desferrioxamine infusion may also be used. Some studies reporting positive results[9,12] have used relatively high doses of desferrioxamine (40 mg/kg) with plasma-aluminium measured 24 to 44 hours later, but there have been concerns about desferrioxamine toxicity.[13] A study[10] using a lower dose of desferrioxamine (28.5 mg/kg) and measuring plasma aluminium 5 hours later found similar increases in patients both with and without bone-aluminium accumulation. However, others have reported[14] that lower doses of desferrioxamine (5 or 10 mg/kg) are adequate when combined with measurement of serum-parathyroid hormone concentrations. The *National Kidney Foundation* guidelines[13] for bone metabolism and disease in chronic kidney disease suggest that when aluminium toxicity is suspected, a test dose of desferrioxamine 5 mg/kg is infused during the last hour of the dialysis session. Serum-aluminium concentrations are measured at baseline and 2 days later, before the next dialysis session; the test is considered positive if the aluminium concentration increases by 50 nanograms/mL or more. Aluminium bone disease is diagnosed when there is a positive desferrioxamine test and serum-parathyroid concentrations below 150 picograms/mL. Desferrioxamine is used to treat aluminium toxicity in symptomatic patients with aluminium concentrations of 60 to 200 nanograms/mL or a positive desferrioxamine test. To avoid desferrioxamine-induced neurotoxicity, patients with a baseline serum-aluminium concentration above 200 nanograms/mL should not have a desferrioxamine test or treatment.

Desferrioxamine therapy has also produced beneficial results in *dialysis patients with anaemia*[15-17] and has also been found to reverse aluminium-induced resistance to erythropoietin.[18,19]

Prurigo nodularis in chronic aluminium overload has responded to desferrioxamine, with resolution of itch and skin lesions.[20]

1. Chang TMS, Barre P. Effect of desferrioxamine on removal of aluminium and iron by coated charcoal haemoperfusion and haemodialysis. *Lancet* 1983; ii: 1051–3.
2. Ackrill P, *et al.* Successful removal of aluminium from patient with dialysis encephalopathy. *Lancet* 1980; ii: 692–3.
3. Arze RS, *et al.* Reversal of aluminium dialysis encephalopathy after desferrioxamine treatment. *Lancet* 1981; ii: 1116.
4. Milne FJ, *et al.* Low aluminium water, desferrioxamine, and dialysis encephalopathy. *Lancet* 1982; ii: 502.
5. Payton CD, *et al.* Successful treatment of aluminium encephalopathy by intraperitoneal desferrioxamine. *Lancet* 1984; i: 1132–3.
6. Altmann P, *et al.* Disturbance of cerebral function by aluminium in haemodialysis patients without overt aluminium toxicity. *Lancet* 1989; ii: 7–12.
7. Nakamura H, *et al.* Acute encephalopathy due to aluminum toxicity successfully treated by combined intravenous deferoxamine and hemodialysis. *J Clin Pharmacol* 2000; 40: 296–300.
8. Brown DJ, *et al.* Treatment of dialysis osteomalacia with desferrioxamine. *Lancet* 1982; ii: 343–5.
9. McCarthy JT, *et al.* Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; 74: 257–76.
10. Malluche HH, *et al.* The use of deferoxamine in the management of aluminum accumulation in bone in patients with renal failure. *N Engl J Med* 1984; 311: 140–4.
11. Kan W-C, *et al.* Comparison of low-dose deferoxamine versus standard-dose deferoxamine for treatment of aluminium overload among haemodialysis patients. *Nephrol Dial Transplant* 2010; 25: 1604–8.
12. Milliner DS, *et al.* Use of deferoxamine infusion test in the diagnosis of aluminium-related osteodystrophy. *Ann Intern Med* 1984; 101: 775–80.
13. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42 (suppl 3): S1–S201. Also available at: http://www.kidney.org/professionals/kdoqi/guidelines_bone/pdf/boneguidelines.pdf (accessed 07/01/11)
14. D'Haese PC, *et al.* Use of the low-dose desferrioxamine test to diagnose and differentiate between patients with aluminium-related bone disease, increased risk for aluminium toxicity, or aluminium overload. *Nephrol Dial Transplant* 1995; 10: 1874–84.
15. de la Serna P-J, *et al.* Improvement in the erythropoiesis of chronic haemodialysis patients with desferrioxamine. *Lancet* 1988; i: 1009–11.
16. Altmann P, *et al.* Aluminium chelation therapy in dialysis patients: evidence for inhibition of haemoglobin synthesis by low levels of aluminium. *Lancet* 1988; i: 1012–15.
17. Padovese P, *et al.* Desferrioxamine versus erythropoietin for treatment of dialysis anaemia. *Lancet* 1990; 335: 1465.
18. Rosenlöf K, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; 335: 247–9.
19. Zachée P, *et al.* Erythropoietin, aluminium, and anaemia in patients on haemodialysis. *Lancet* 1990; 335: 1038–9.
20. Brown MA, *et al.* Prurigo nodularis and aluminium overload in maintenance haemodialysis. *Lancet* 1992; 340: 48.

Iron overload. Chronic iron overload can be caused by inappropriately increased gastrointestinal absorption, by grossly excessive oral intake over long periods, or by parenteral administration of iron, for example from transfused blood.[1,2] Excess iron is stored in the form of ferritin and haemosiderin. The term **haemosiderosis** is applied to the accumulation of haemosiderin in body tissues without associated tissue damage; **haemochromatosis** refers to a chronic disease state in which iron overload leads to tissue damage, mainly in the heart, liver, and pancreas.

Primary or hereditary haemochromatosis is caused by a genetic defect in iron metabolism that results in excessive gastrointestinal absorption of iron. The treatment of choice for primary haemochromatosis is phlebotomy,[1-7] but chelation therapy may be needed in patients with anaemia, hypoproteinaemia, or severe cardiac disease. Other management strategies include dietary modification to reduce iron absorption; gastric-acid suppressing drugs such as proton pump inhibitors have been investigated as a means of reducing gastrointestinal absorption of iron.[5]

Neonatal haemochromatosis is a rare condition of unknown cause and results in fetal death or severe liver injury. Antoxidants and iron chelators may improve prognosis,[8] but many infants require liver transplantation. Maternal treatment with normal immunoglobulins has been reported[9] to reduce the severity of recurrent neonatal haemochromatosis, and normal immunoglobulin with exchange transfusion has been used successfully in a small number of neonates on the first day of life, reducing the need for liver transplantation.[10]

Secondary or acquired haemochromatosis is commonly associated with chronic anaemias, in particular thalassaemia, in which excessive iron uptake due to disordered erythropoiesis and excess iron from repeated blood transfusions contribute to iron overload.[1,2] These patients generally require iron chelation, usually with parenteral desferrioxamine although oral iron chelators such as deferasirox and deferiprone have also been used (see below).

1. Porter JB. Practical management of iron overload. *Br J Haematol* 2001; 115: 239–52.
2. Barton JC. Optimal management strategies for chronic iron overload. *Drugs* 2007; 67: 685–700.
3. Yen AW, *et al.* Revisiting hereditary hemochromatosis: current concepts and progress. *Am J Med* 2006; 119: 391–9.
4. Adams PC, Barton JC. Haemochromatosis. *Lancet* 2007; 370: 1855–60.
5. Adams PC, Barton JC. How I treat hemochromatosis. *Blood* 2010; 116: 317–25.
6. Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology* 2010; 139: 393–408.
7. Franchini M. Hereditary iron overload: update on pathophysiology, diagnosis, and treatment. *Am J Hematol* 2006; 81: 202–9.
8. Flynn DM, *et al.* Progress in treatment and outcome for children with neonatal haemochromatosis. *Arch Dis Child Fetal Neonatal Ed* 2003; 88: F124–F127.
9. Whitington PF, Hibbard JU. High-dose immunoglobulin during pregnancy for recurrent neonatal haemochromatosis. *Lancet* 2004; 364: 1690–8.
10. Rand EB, *et al.* Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. *J Pediatr* 2009; 155: 566–71.

THALASSAEMIA. Patients homozygous for β-thalassaemia (p. 1124.1) have severe anaemia requiring regular blood transfusions. As a consequence of this treatment iron overload develops and the excessive deposition of iron in the myocardium usually results in these patients dying in their second or third decade from arrhythmias or cardiac failure. Iron chelators such as desferrioxamine are therefore used to retard the accumulation of iron.

Desferrioxamine has been shown to prevent complications and improve survival in thalassaemic patients given regular systemic therapy.[1-5] There is also some evidence that impaired organ function might improve with intensive therapy. The liver is the main site of iron accumulation in iron overload, and a reduction in liver-iron concentrations and improvement in liver function has been reported[6] in patients with transfusional iron overload treated with desferrioxamine 2 to 4 g by slow subcutaneous infusion over 12 hours on 6 nights a week. However, in another study[7] improvement in the degree of hepatic fibrosis was seen after 3 to 5 years in only 2 of 7 patients given desferrioxamine up to 85 mg/kg daily by subcutaneous injection, despite reductions in iron concentrations. Preservation or possibly improvement in cardiac function has also been reported,[8-10] although cardiac disease continues to be the main cause of death in patients with thalassaemia. Although initial studies used intramuscular treatment, increased iron excretion is seen with continuous subcutaneous infusion, and this is usually the preferred route. However, compliance may be a problem, and is a major determinant of the efficacy of treatment.[2] Intensive intravenous therapy, using continuous infusion devices, has been used successfully[11] in patients inadequately treated with subcutaneous desferrioxamine, and good results have also been reported[12,13] with intermittent intravenous infusions. Subcutaneous bolus injection has also been used (see Administration, p. 1544.3) although it may not be tolerated in all patients. Better iron excretion may be achieved if patients are given daily supplements of oral ascorbic acid in addition to desferrioxamine (but see under Interactions, p. 1547.3). The most appropriate time to start desferrioxamine is not clear. Beginning chelation therapy before puberty could help to ensure normal sexual development in patients with thalassaemia major.[14] Other studies[1,2] have reported that starting therapy before severe iron overload develops, and maintaining low serum-ferritin concentrations, prevents cardiac disease and improves prognosis, suggesting that chelation therapy should be started as early as possible, to prevent organ damage developing. However, desferrioxamine has been associated with adverse effects on growth (see Effects on Growth Rate, p. 1547.1) and it is usual to delay therapy until children are about 3 years of age, when iron overload becomes significant, although earlier treatment may be required in some cases.[3]

Alternatives to desferrioxamine have also been investigated. Deferiprone, which is given orally, effectively reduces iron overload,[5,15] but its long-term benefits are controversial. A study[16] in patients with thalassaemia reported progression of hepatic fibrosis in patients given deferiprone, although another study[17] was unable to confirm these findings. Other studies[18-20] have suggested that deferiprone may be superior to desferrioxamine in reducing cardiac complications. A systematic review[21] found no evidence to change treatment recommendations that indicate deferiprone for use in those for whom desferrioxamine is contra-indicated or ineffective; the authors acknowledged that there was a need for more research. It has been suggested that treatment with desferrioxamine and deferiprone may have an additive effect, and it has been widely studied.[22-25] One study reported a reduction in myocardial iron and an improvement in ejection fraction and endothelial function with the combination compared with desferrioxamine alone;[22] increased survival has also been seen with intensive combined treatment.[26] However, despite the increased chelating ability of the combination, another study did not find sequential use to improve survival.[27] Deferasirox, another oral iron chelator, is also used;[28] it may, however, be less effective than deferiprone in reducing cardiac complications.[20] Deferasirox has also been combined with desferrioxamine in the hope of improved efficacy.[29]

1. Olivieri NF, *et al.* Survival in medically treated patients with homozygous β-thalassemia. *N Engl J Med* 1994; 331: 574–8.
2. Brittenham GM, *et al.* Efficacy of deferoxamine in preventing complications of iron overload in patients with thalassemia major. *N Engl J Med* 1994; 331: 567–73.
3. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. *Blood* 1997; 89: 739–61.
4. Roberts D, *et al.* Desferrioxamine mesylate for managing transfusional iron overload in people with transfusion-dependent thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 09/12/09).
5. Maggio A. Light and shadows in the iron chelation treatment of haematological diseases. *Br J Haematol* 2007; 138: 407–21.
6. Hoffbrand AV, *et al.* Improvement in status and liver function in patients with transfusional iron overload with long-term subcutaneous desferrioxamine. *Lancet* 1979; i: 947–9.
7. Maurer HS, *et al.* A prospective evaluation of iron chelation therapy in children with severe β-thalassemia: a six-year study. *Am J Dis Child* 1988; 142: 287–92.
8. Freeman AP, *et al.* Early left ventricular dysfunction and chelation therapy in thalassemia major. *Ann Intern Med* 1983; 99: 450–4.
9. Marcus RE, *et al.* Desferrioxamine to improve cardiac function in iron-overloaded patients with thalassaemia major. *Lancet* 1984; i: 392–3.
10. Wolfe L, *et al.* Prevention of cardiac disease by subcutaneous deferoxamine in patients with thalassemia major. *N Engl J Med* 1985; 312: 1600–3.
11. Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk β-thalassemia. *Blood* 2000; 95: 1229–36.
12. Hagège I, *et al.* Long-term administration of high-dose deferoxamine 2 days per week in thalassemic patients. *Eur J Haematol* 2001; 67: 230–1.
13. Miskin H, *et al.* Reversal of cardiac complications in thalassemia major by long-term intermittent daily intensive iron chelation. *Eur J Haematol* 2003; 70: 398–403.
14. Bronspiegel-Weintrob N, *et al.* Effect of age at the start of iron chelation therapy on gonadal function in β-thalassemia major. *N Engl J Med* 1990; 323: 713–19.
15. Addis A, *et al.* Meta-analytic review of the clinical effectiveness of oral deferiprone (L_1). *Eur J Clin Pharmacol* 1999; 55: 1–6.
16. Olivieri NF, *et al.* Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *N Engl J Med* 1998; 339: 417–23.
17. Wanless IR, *et al.* Lack of progressive hepatic fibrosis during long-term therapy with deferiprone in subjects with transfusion-dependent beta-thalassemia. *Blood* 2002; 100: 1566–9.
18. Anderson LJ, *et al.* Comparison of effects of oral deferiprone and subcutaneous desferrioxamine on myocardial iron concentrations and ventricular function in beta-thalassaemia. *Lancet* 2002; 360: 516–20.
19. Piga A, *et al.* Comparative efficacy of deferiprone and deferoxamine on survival and cardiac disease in patients with thalassemia major: a retrospective analysis. *Haematologica* 2003; 88: 489–96.
20. Pepe A, *et al.* Deferasirox, deferiprone and desferrioxamine treatment in thalassemia major patients: cardiac iron and function comparison

determined by quantitative magnetic resonance imaging. *Haematologica* 2011; 96: 41–7.
21. Roberts D, *et al.* Oral deferiprone for iron chelation in people with thalassaemia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/07).
22. Tanner MA, *et al.* A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. *Circulation* 2007; 115: 1876–84.
23. Tsiapras D, *et al.* Effect of combined chelation therapy with deferiprone and deferoxamine on left ventricular diastolic function in adult β-thalassemia major patients. *Hemoglobin* 2010; 34: 210–20.
24. Ricchi P, *et al.* Combined chelation therapy in thalassemia major with deferiprone and desferrioxamine: a retrospective study. *Eur J Haematol* 2010; 85: 36–42.
25. Drakonaki EE, *et al.* Deferoxamine versus combined therapy for chelating liver, spleen and bone marrow iron in β-thalassemic patients: a quantitative magnetic resonance imaging study. *Hemoglobin* 2010; 34: 95–106.
26. Lai ME, *et al.* Increased survival and reversion of iron-induced cardiac disease in patients with thalassemia major receiving intensive combined chelation therapy as compared to desferoxamine alone. *Blood Cells Mol Dis* 2010; 45: 136–9.
27. Maggio A, *et al.* Long-term sequential deferiprone-deferoxamine versus deferiprone alone for thalassaemia major patients: a randomized clinical trial. *Br J Haematol* 2009; 145: 245–54.
28. Pennell DJ, *et al.* Efficacy of deferasirox in reducing and preventing cardiac iron overload in β-thalassemia. *Blood* 2010; 115: 2364–71.
29. Jetsrisuparb A, *et al.* Retrospective study on the combination of desferrioxamine and deferasirox for treatment of iron-overloaded thalassemic patients: first evidence of more than 2 years. *J Pediatr Hematol Oncol* 2010; 32: 400–3.

Iron poisoning. Diagnosis of acute iron poisoning relies on the history, clinical symptoms, and serum-iron concentrations. An intramuscular desferrioxamine challenge test has also been used; if free iron is present, ferrioxamine will be excreted in the urine imparting a classic 'vin rosé' colour. However, interpretation is difficult and a negative result does not rule out toxicity; the test is no longer generally recommended.

The management of acute iron poisoning (see Treatment of Adverse Effects, under Iron, p. 2074.2) involves supportive care and parenteral desferrioxamine for severe toxicity. Although addition of desferrioxamine to gastric lavage fluid has been suggested there is little evidence of efficacy and some concern over possible toxic effects of ferrioxamine.

Malaria. Following the suggestion that iron-deficiency anaemia may offer some protection against infections (see Infections in the Precautions for Iron, p. 2074.3), desferrioxamine was tried in a few patients with malaria.[1,2] Any antimalarial effect of desferrioxamine was thought to be as a result of chelation of parasite-associated iron rather than reduction in body-iron concentrations in the patient. Desferrioxamine given intravenously was reported[3] to shorten the time to regain consciousness in children with cerebral malaria receiving standard therapy with intravenous quinine and oral pyrimethamine-sulfadoxine. However, in another study[4] there was no evidence of a beneficial effect on mortality when desferrioxamine was added to an antimalarial treatment regimen that included a loading dose of quinine. Deferiprone has also been studied,[5,6] with mixed results. A systematic review[7] considered that although there were some positive results with desferrioxamine and deferiprone, there were insufficient data to draw conclusions about efficacy. The potential for adverse effects and the need for parenteral administration of desferrioxamine was also deemed likely to limit their use for malaria. The use of desferrioxamine in the treatment of malaria is not recommended by WHO.[8]

1. Gordeuk VR, *et al.* Iron chelation as a chemotherapeutic strategy for falciparum malaria. *Am J Trop Med Hyg* 1993; 48: 193–7.
2. Thompson DF. Deferoxamine treatment of malaria. *Ann Pharmacother* 1994; 28: 602–3.
3. Gordeuk V, *et al.* Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria. *N Engl J Med* 1992; 327: 1473–7.
4. Thuma PE, *et al.* Effect of iron chelation therapy on mortality in Zambian children with cerebral malaria. *Trans R Soc Trop Med Hyg* 1998; 92: 214–18.
5. Thuma PE, *et al.* Assessment of the effect of the oral iron chelator deferiprone on asymptomatic Plasmodium falciparum parasitemia in humans. *Am J Trop Med Hyg* 1998; 58: 358–64.
6. Mohanty D, *et al.* Deferiprone (L1) as an adjuvant therapy for Plasmodium falciparum malaria. *Indian J Med Res* 2002; 115: 17–21.
7. Smith EJ, Meremikwu MM. Iron chelating agents for treating malaria. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 11/01/11).
8. WHO. *Guidelines for the treatment of malaria.* 2nd ed. Geneva: WHO. 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf (accessed 31/08/10)

Porphyria. The management of various forms of porphyria is discussed on p. 1556.1. Desferrioxamine has been used to reduce serum-iron concentrations in porphyria cutanea tarda and may have a role if phlebotomy is contra-indicated. In a study of 25 patients with porphyria cutanea tarda,[1] subcutaneous infusion of desferrioxamine was found to be as effective as repeated phlebotomies in normalising porphyrin excretion and iron storage. Intravenous desferrioxamine was also used successfully to treat porphyria cutanea tarda,[2] including haemodialysis-related disease;[3-5] however, intramuscular use was ineffective.[6]

1. Rocchi E, *et al.* Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion. *Br J Dermatol* 1986; 114: 621–9.
2. Rocchi E, *et al.* High weekly intravenous doses of desferrioxamine in porphyria cutanea tarda. *Br J Dermatol* 1987; 117: 393–6.
3. Praga M, *et al.* Treatment of hemodialysis-related porphyria cutanea tarda with deferoxamine. *N Engl J Med* 1987; 316: 547–8.
4. Labidi J. Porphyria cutanea tarda in a chronic hemodialysis patient. *Saudi J Kidney Dis Transpl* 2010; 21: 919–22.
5. Pitche P, *et al.* Porphyrie cutanée tardive chez l'hémodialysé. Un cas sévère traité efficacement par déféroxamine. *Ann Dermatol Venereol* 2003; 130: 37–9.
6. Muñoz JJ, *et al.* Desferrioxamine in the treatment of porphyria tarda: ineffectiveness of intramuscular administration. *J Dermatol* 1990; 17: 329–31.

Stroke. Desferrioxamine has been investigated[1,2] for its potential value in reducing local neurotoxicity after intracerebral haemorrhage (p. 1269.2).

1. Hua Y, *et al.* Deferoxamine therapy for intracerebral hemorrhage. *Acta Neurochir Suppl* 2008; 105: 3–6.
2. Selim M. Deferoxamine mesylate: a new hope for intracerebral hemorrhage: from bench to clinical trials. *Stroke* 2009; 40 (3 suppl): S90–S91.

Adverse Effects, Treatment, and Precautions

Rapid intravenous injection of desferrioxamine may cause flushing, urticaria, tachycardia, hypotension, and shock. Injection-site reactions include pain, swelling, pruritus, and erythema, and may be associated with systemic adverse effects including arthralgia, myalgia, fever, headache, bronchospasm, and gastrointestinal disorders. Other allergic reactions include rash, angioedema, and anaphylaxis.

Blood dyscrasias such as thrombocytopenia, leucopenia, and aplastic anaemia have occurred, as have hepatic dysfunction and increases in liver enzymes. Acute respiratory distress syndrome has been reported after treatment with high-dose intravenous desferrioxamine. Desferrioxamine treatment of aluminium overload has resulted in hypocalcaemia and aggravation of hyperparathyroidism.

Bone disorders such as metaphyseal dysplasia and impaired growth have been seen in young children or those given inappropriately high doses of desferrioxamine and regular checks on height and weight are recommended for children. A reduction in dose may restore growth rate. Muscle spasms and bone pain can also occur.

Nervous system disorders include dizziness, peripheral neuropathy, and paraesthesia. Desferrioxamine may exacerbate aluminium-related encephalopathy and precipitate seizures. Prophylactic treatment with antiepileptics such as clonazepam has been suggested for patients judged to be at risk. Visual and auditory disturbances have been reported, usually when desferrioxamine is given at high doses, for prolonged periods, or in patients with low ferritin concentrations. Hearing loss and tinnitus are uncommon and visual disturbances (including retinal changes, cataracts, optic neuritis, and impaired peripheral, colour, and night vision) are rare; these disturbances are usually reversible if desferrioxamine is withdrawn. Regular ophthalmological and audiological examinations are recommended for patients on long-term therapy.

Caution is required when using desferrioxamine in patients with renal impairment as the metal complex is excreted by the kidneys. The desferrioxamine-iron complex may colour the urine red or brown. Dysuria, increases in serum-creatinine, renal tubular disorders, and acute renal failure have been reported during treatment.

An increased susceptibility to infection, particularly with *Yersinia* species, has been reported in patients with iron overload; desferrioxamine therapy may sometimes exacerbate this. Severe fungal infections, including some fatalities, have also been reported, mainly in patients undergoing dialysis. If infection is suspected, treatment with desferrioxamine should be stopped and appropriate antimicrobial treatment given. Desferrioxamine may be restarted once the infection has been cleared.

The adverse effects of desferrioxamine generally respond to dosage reduction. In acute overdosage desferrioxamine may be removed by haemodialysis. The urinary excretion of iron should be measured regularly during treatment for iron overload, and the serum concentration of aluminium monitored during the management of aluminium overload. Monitoring of cardiac function is also recommended in those receiving combined treatment with ascorbic acid (see also Interactions, p. 1547.3).

Aluminium encephalopathy. Desferrioxamine may be used in the management of aluminium-associated encephalopathy, but has also been associated with precipitation or exacerbation of dementia,[1-3] with some fatal outcomes,[1] in dialysis patients with aluminium overload. It has been suggested[2] that the effect could be dose related. Desferrioxamine mobilises stored aluminium and may therefore increase plasma-aluminium concentrations, leading to toxicity. Use of a low dose of desferrioxamine (for example, 10 mg/kg) shortly before dialysis, in addition to charcoal haemoperfusion, has been recommended.[1] However, exacerbation of aluminium encephalopathy has also been reported[3] after the low dose of 500 mg twice weekly.

1. Sherrard DJ, *et al.* Precipitation of dialysis dementia by deferoxamine treatment of aluminum related bone disease. *Am J Kidney Dis* 1988; 12: 126–30.
2. McCauley J, Sorkin I. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; 4: 110–14.
3. Lillevang ST, Pedersen FB. Exacerbation of aluminium encephalopathy after treatment with desferrioxamine. *Nephrol Dial Transplant* 1989; 4: 676.

Breast feeding. It is unknown whether desferrioxamine is excreted in breast milk. There are case reports describing the use of desferrioxamine in breast-feeding mothers,[1,2] without significant disturbance of iron metabolism in the infant.[1] However, data are scarce and licensed product information recommends that the drug should only be used if the benefits of treatment are considered to outweigh the risks.

1. Surbek DV, *et al.* Pregnancy and lactation in homozygous β-thalassemia major. *J Perinat Med* 1998; 26: 240–3.
2. Pafumi C, *et al.* Pregnancy outcome of a transfusion-dependent thalassemic woman. *Ann Hematol* 2000; 79: 571–3.

Diagnostic tests. *In vitro* and *animal* studies[1] have suggested that desferrioxamine could interfere with estimations of total iron-binding capacity. It may also interfere with colorimetric iron assays.

Desferrioxamine also binds gallium and has been reported[2-4] to distort the results of gallium-67 imaging studies. Licensed product information recommends stopping desferrioxamine 48 hours before scintigraphy.

1. Bentur Y, *et al.* Misinterpretation of iron-binding capacity in the presence of deferoxamine. *J Pediatr* 1991; 118: 139–42.
2. Nagamachi S, *et al.* Gallium-67 scintigraphy in patients with hemochromatosis treated by deferoxamine. *Ann Nucl Med* 1988; 2: 35–9.
3. Baker DL, Manno CS. Rapid excretion of gallium-67 isotope in an iron-overloaded patient receiving high-dose intravenous deferoxamine. *Am J Hematol* 1988; 29: 230–2.
4. Brown SJ, *et al.* Altered biodistribution of gallium-67 in a patient with aluminum toxicity treated with desferoxamine. *J Nucl Med* 1990; 31: 115–17.

Effects on the blood. A patient with end-stage renal disease developed reversible thrombocytopenia on 3 separate occasions after intravenous infusions of desferrioxamine for dialysis osteomalacia.[1] Acute fatal aplastic anaemia occurred in a 16-year-old girl with thalassaemia after high intravenous doses of desferrioxamine (80 mg/kg daily) for 20 days.[2]

1. Walker JA, *et al.* Thrombocytopenia associated with intravenous desferrioxamine. *Am J Kidney Dis* 1985; 6: 254–6.
2. Sofroniadou K, *et al.* Acute bone marrow aplasia associated with intravenous administration of deferoxamine (desferrioxamine). *Drug Safety* 1990; 5: 152–4.

Effects on the ears and eyes. Lens opacities, optic neuropathy, retinal pigmentary changes and other retinal abnormalities, and ocular disturbances including loss of colour vision, night blindness, decreased visual acuity, and field defects, have been reported in patients receiving long-term or high-dose treatment with desferrioxamine.[1-4] Irreversible ocular toxicity has also occurred after a single intravenous dose to test for aluminium overload in a patient with chronic renal failure on dialysis.[5] Studies have reported widely differing rates; in 2 studies long-term use of desferrioxamine was associated with symptomatic or asymptomatic ocular changes in 4% (2 of 52)[1] and 66% (10 of 15)[6] of patients respectively.

Sensorineural hearing impairment has also been reported,[1,7] and in one study[8] was attributed to desferrioxamine in 29% of patients (22 of 75).

The mechanism by which desferrioxamine causes neurotoxicity is unclear. Some studies[3,6] have suggested that depletion of trace metals, particularly zinc or copper, may be involved; other studies[7,9] have found an association with dose, suggesting a direct toxic effect of desferrioxamine. Low serum-ferritin concentrations may be a risk factor for ototoxicity, and it has been suggested that the risk may be minimised by adjusting the desferrioxamine dose according to serum-ferritin concentrations, to achieve a therapeutic index below 0.025 (calculated by dividing the daily dose in mg/kg by the serum-ferritin concentration in micrograms/litre);[9] this therapeutic index has also been used in patients with ocular toxicity.[4] Reported risk factors for visual loss in desferrioxamine retinopathy include blood-retinal barrier breakdown associated with diabetes and rheumatoid arthritis, metabolic encephalopathy, and renal failure.[2] Both ophthalmic and auditory abnormalities can improve when desferrioxamine is withdrawn,[1,2,6] although sometimes the effects may be irreversible[4] or recovery may only be partial.[2] Hearing loss associated with desferrioxamine therapy remained stable or worsened in some patients when treatment was changed to deferiprone, see Effects on the Ears and Eyes, under Deferiprone, p. 1543.3.

There has also been a report[10] of improvement following use of zinc supplements.

1. Cohen A, *et al.* Vision and hearing during deferoxamine therapy. *J Pediatr* 1990; 117: 326–30.
2. Halmovici R, *et al.* Deferoxamine Retinopathy Study Group. The expanded clinical spectrum of deferoxamine retinopathy. *Ophthalmology* 2002; 109: 164–71.
3. Genead MA, *et al.* Macular vitelliform lesion in desferrioxamine-related retinopathy. *Doc Ophthalmol* 2010; 121: 161–6.
4. Lai TYY, *et al.* Rapid development of severe toxic retinopathy associated with continuous intravenous deferoxamine infusion. *Br J Opthalmol* 2006; 90: 243–4.
5. Bene C, *et al.* Irreversible ocular toxicity from single "challenge" dose of deferoxamine. *Clin Nephrol* 1989; 31: 45–8.
6. De Virgillis S, *et al.* Depletion of trace elements and acute ocular toxicity induced by desferrioxamine in patients with thalassaemia. *Arch Dis Child* 1988; 63: 250–5.
7. Karimi M, *et al.* Evaluation of the incidence of sensorineural hearing loss in beta-thalassemia major patients under regular chelation therapy with desferrioxamine. *Acta Haematol (Basel)* 2002; 108: 79–83.
8. Chiodo AA, *et al.* Desferrioxamine ototoxicity in an adult transfusion-dependent population. *J Otolaryngol* 1997; 26: 116–22.
9. Porter JB, *et al.* Desferrioxamine ototoxicity: evaluation of risk factors in thalassaemic patients and guidelines for safe dosage. *Br J Haematol* 1989; 73: 403–9.
10. Pinna A, *et al.* Rapid recovery with oral zinc sulphate in deferoxamine-induced presumed optic neuropathy and hearing loss. *J Neuroophthalmol* 2001; 21: 32–3.

Effects on growth rate. Growth retardation has been noted in thalassaemic children undergoing desferrioxamine therapy,[1-3] and bone dysplasia has occurred even with subcutaneous doses of no more than 50 mg/kg daily, with the metaphysis of the distal ulna commonly affected.[3] Growth retardation was related to dose[1,2] and inversely related to iron stores.[1] It was greater in those who started receiving desferrioxamine at the start of transfusion therapy at about 9 months old than in those who started desferrioxamine once iron accumulation was established, after about 3 years. A sharp increase in growth velocity was reported in 15 patients with low ferritin levels after a 50% reduction in desferrioxamine dose.[1]

1. Piga A, *et al.* High-dose desferrioxamine as a cause of growth failure in thalassaemic patients. *Eur J Haematol* 1988; 40: 380–1.
2. De Virgillis S, *et al.* Deferoxamine-induced growth retardation in patients with thalassemia major. *J Pediatr* 1988; 113: 661–9.
3. Chan YL, *et al.* Desferrioxamine-induced long bone changes in thalassaemic patients — radiographic features, prevalence and relations with growth. *Clin Radiol* 2000; 55: 610–14.

Effects on the kidneys. Intensive treatment with intravenous infusions of desferrioxamine has been associated[1,2] with acute decreases in renal function, and it has been suggested[3] that nephrotoxicity could be related to the high doses used; acute renal failure has also been reported[4,5] after intravenous overdosage of desferrioxamine. However, other studies[6-9] have also found reductions in renal function associated with more usual subcutaneous dosage regimens. Renal function generally improved once desferrioxamine was stopped. Two mechanisms have been proposed for desferrioxamine-induced kidney damage: inhibition of prostaglandin synthesis causing an acute decrease in renal perfusion in the absence of systemic blood pressure changes, or inhibition of tubular resorption resulting in solute diuresis.[2]

1. Batey R, *et al.* Acute renal insufficiency occurring during intravenous desferrioxamine therapy. *Scand J Haematol* 1979; 22: 277–9.
2. Koren G, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1989; 143: 1077–80.
3. Li Volti S, *et al.* Acute changes in renal function associated with deferoxamine therapy. *Am J Dis Child* 1990; 144: 1069–70.
4. Cianciulli P, *et al.* Acute renal failure occurring during intravenous desferrioxamine therapy: recovery after haemodialysis. *Haematologica* 1992; 77: 514–15.
5. Prasannan L, *et al.* Acute renal failure following deferoxamine overdose. *Pediatr Nephrol* 2003; 18: 283–5.
6. Koren G, Bentur Y. Acute changes in renal function associated with deferoxamine. *Am J Dis Child* 1990; 144: 1070.
7. Cianciulli P, *et al.* Early detection of nephrotoxic effects in thalassemic patients receiving desferrioxamine therapy. *Kidney Int* 1994; 46: 467–70.
8. Clajus C, *et al.* Acute kidney injury due to deferoxamine in a renal transplant patient. *Nephrol Dial Transplant* 2008; 23: 1061–4.
9. Hamed EA, ElMelegy NT. Renal functions in pediatric patients with beta-thalassemia major: relation to chelation therapy: original prospective study. *Ital J Pediatr* 2010; 36: 39.

Effects on the lungs. Pulmonary complications, including fatal acute respiratory distress syndrome, have been reported in patients given prolonged or high-dose intravenous desferrioxamine. A pulmonary syndrome with tachypnoea, hypoxaemia, reduced pulmonary function, and evidence of diffuse interstitial fibrosis and inflammation, has been reported[1-4] with high doses for thalassaemia or acute iron poisoning. There has also been a report[5] of fatal acute respiratory distress syndrome in 4 patients given intravenous desferrioxamine for 65 to 92 hours for acute iron poisoning; toxicity was attributed to the prolonged infusion since no pulmonary complications had been noted with desferrioxamine given for less than 24 hours. Subsequent correspondence, however, suggested alternative explanations for the pulmonary injury such as the use of doses above the daily maximum,[6] or a direct effect of acute iron intoxication following inadequate desferrioxamine therapy.[7] Other proposed mechanisms for the pulmonary injury include generation of free radicals leading to oxidative damage,[3-5,8] or a hypersensitivity reaction,[1,2] although some patients who had pulmonary symptoms with intravenous therapy tolerated subcutaneous treatment.[1,3]

1. Freedman MH, *et al.* Pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine infusions. *Am J Dis Child* 1990; 144: 565–9.
2. Scanderbeg AC, *et al.* Pulmonary syndrome and intravenous high-dose desferrioxamine. *Lancet* 1990; 336: 1511.
3. Rego EM, *et al.* Dose-dependent pulmonary syndrome in patients with thalassemia major receiving intravenous deferoxamine. *Am J Hematol* 1998; 58: 340–1.
4. Ioannides AS, Panisello JM. Acute respiratory distress syndrome in children with acute iron poisoning: the role of intravenous desferrioxamine. *Eur J Pediatr* 2000; 159: 158–9.
5. Tenenbein M, *et al.* Pulmonary toxic effects of continuous desferrioxamine administration in acute iron poisoning. *Lancet* 1992; 339: 699–701.
6. Macarol V, Yawalkar SJ. Desferrioxamine in acute iron poisoning. *Lancet* 1992; 339: 1601.
7. Shannon M. Desferrioxamine in acute iron poisoning. *Lancet* 1992; 339: 1601.
8. Helson L, *et al.* Desferrioxamine in acute iron poisoning. *Lancet* 1992; 339: 1602–3.

Effects on the skin. Desferrioxamine may be used in the management of porphyria cutanea tarda (see p. 1556.1). However, lesions resembling porphyria cutanea tarda developed in 3 patients during long-term therapy with desferrioxamine for aluminium toxicity.[1] The lesions worsened on exposure to sun and resolved when treatment was completed. It was also possible that the lesions were associated with aluminium accumulation. Alopecia was noted in 1 patient but an association with desferrioxamine could not be established.

1. McCarthy JT, *et al.* Clinical experience with desferrioxamine in dialysis patients with aluminium toxicity. *Q J Med* 1990; 74: 257–76.

Hypersensitivity. Individual cases of anaphylactoid reactions have been reported with desferrioxamine given by various parenteral routes, and desensitisation has been carried out successfully in some patients.[1-5] Immunological studies have suggested that the reaction may be pseudo-allergic in nature;[2-4] 4 patients who were unable to tolerate subcutaneous desferrioxamine due to severe hypersensitivity reactions were successfully treated with high-dose intravenous therapy.[6]

Effects on the lungs have also been attributed to hypersensitivity (see above).

1. Miller KB, *et al.* Rapid desensitisation for desferrioxamine anaphylactic reaction. *Lancet* 1981; i: 1059.
2. Bousquet J, *et al.* Rapid desensitisation for desferrioxamine anaphylactoid reactions. *Lancet* 1983; ii: 859–60.
3. Patriarca G, *et al.* Successful desensitization of a child with desferrioxamine hypersensitivity. *J Investig Allergol Clin Immunol* 1995; 5: 294–5.
4. La Rosa M, *et al.* Desensitization treatment for anaphylactoid reactions to desferrioxamine in a pediatric patient with thalassemia. *J Allergy Clin Immunol* 1996; 97: 127–8.
5. Gülen F, *et al.* Successful desensitization of a case with desferrioxamine hypersensitivity. *Minerva Pediatr* 2006; 58: 571–4.
6. Lombardo T, *et al.* High-dose intravenous desferrioxamine (DFO) delivery in four thalassemic patients allergic to subcutaneous DFO administration. *Am J Hematol* 1996; 51: 90–2.

Infection susceptibility. *Yersinia enterocolitica* is one of the most iron-dependent of all microbes and the risk of infection is increased in patients with iron overload. Use of exogenous iron-binding compounds (siderophores) such as desferrioxamine, may increase the ability of *Y. enterocolitica* to take up iron and may contribute to the increased risk of infection. Infections due to *Y. enterocolitica* (p. 186.2) have been reported in patients receiving desferrioxamine for acute iron overdosage[1] or for chronic iron overload.[2-5] Severe infection with *Y. pseudotuberculosis* has also been reported in a thalassaemic patient on long-term desferrioxamine therapy.[6]

Treatment with desferrioxamine may also increase susceptibility to mucormycosis. Infections have occurred both in patients with iron overload disorders[7-10] and in those who do not have excessive iron stores.[11-13] A review[8] of 26 cases of mucormycosis in patients undergoing treatment revealed that 23 patients died; in 19 cases the diagnosis was only made at necropsy and only 9 patients received potentially effective treatment (surgery and/or amphotericin B). The organisms responsible were *Rhizopus* species in 13 cases and *Cunninghamella bertholletiae* in 3. In another review of 24 cases of mucormycosis in patients on dialysis,[14] at least 21 were receiving desferrioxamine; infection was fatal in 21 of the 24 patients.

In view of the serious nature of these infections it is important that they should be recognised and treated promptly. It has been suggested that a short course of a suitable antibacterial could be given as prophylaxis to young children from areas with a high incidence of yersiniosis who require treatment with desferrioxamine.[15]

1. Melby K, *et al.* Septicaemia due to Yersinia enterocolitica after oral overdoses of iron. *BMJ* 1982; 285: 467–8.
2. Schametzky M, *et al.* Prophylaxis of systemic yersinosis in thalassaemia major. *Lancet* 1984; i: 791.
3. Chiu HY, *et al.* Infection with Yersinia enterocolitica in patients with iron overload. *BMJ* 1986; 292: 97.
4. Kelly D, *et al.* Yersinia and iron overload. *BMJ* 1986; 292: 413.
5. Gallant T, *et al.* Yersinia sepsis in patients with iron overload treated with deferoxamine. *N Engl J Med* 1986; 314: 1643.
6. Gordts B, *et al.* Yersinia pseudotuberculosis septicaemia in thalassaemia major. *Lancet* 1984; i: 41–2.
7. Sane A, *et al.* Deferoxamine treatment as a risk factor for zygomycete infection. *J Infect Dis* 1989; 159: 151–2.
8. Daly AL, *et al.* Mucormycosis: association with deferoxamine therapy. *Am J Med* 1989; 87: 468–71.
9. Kubota N, *et al.* A massive intraventricular thrombosis by disseminated mucormycosis in a patient with myelodysplastic syndrome during deferoxamine therapy. *Haematologica* 2003; 88: 117–18.
10. Reyes HM, *et al.* Pulmonary invasive mucormycosis in a patient with secondary iron overload following deferoxamine therapy. *Proc (Bayl Univ Med Cent)* 2008; 21: 378–81.
11. Goodill JJ, Abuelo JG. Mucormycosis–a new risk of deferoxamine therapy in dialysis patients with aluminum or iron overload? *N Engl J Med* 1987; 316: 54.
12. Windus DW, *et al.* Fatal rhizopus infections in hemodialysis patients receiving deferoxamine. *Ann Intern Med* 1987; 107: 678–80.
13. Boelaert JR, *et al.* Mucormycosis infections in dialysis patients. *Ann Intern Med* 1987; 107: 782–3.
14. Boelaert JR, *et al.* Mucormycosis among patients on dialysis. *N Engl J Med* 1989; 321: 190–1.
15. Hadjiminas JM. Yersiniosis in acutely iron-loaded children treated with desferrioxamine. *J Antimicrob Chemother* 1988; 21: 680–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desferrioxamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1] Indeed, desferrioxamine may be used in the management of porphyria cutanea tarda to reduce iron concentrations (see p. 1546.1).

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 02/09/11)

Pregnancy. Desferrioxamine has been associated with fetal abnormalities in some *animal* studies, and licensed product information recommends use in pregnancy only if the benefits are considered to outweigh the risks. A review[1] of pregnancy outcome after iron overdose found that of 66 patients reported to the UK Teratology Information Service, 35 of whom had received desferrioxamine, 7 gave birth to infants with malformations (severe in one). However, in each case overdosage had occurred after the first trimester and the malformations therefore could not be directly related to either iron or desferrioxamine. It was concluded that treatment of iron overdose with desferrioxamine should not be withheld solely on the grounds of pregnancy. Long-term use of desferrioxamine has also been reported in pregnant patients with thalassaemia; a case report[2] and review of the literature found no evidence of teratogenicity despite use at various stages of gestation, suggesting that desferrioxamine may be given to the mother if necessary.

1. McElhatton PR, *et al.* Outcome of pregnancy following deliberate iron overdose by the mother. *Hum Exp Toxicol* 1993; 12: 579.
2. Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? *Am J Hematol* 1999; 60: 24–6.

Interactions

Ascorbic acid is often given in addition to desferrioxamine to patients with iron overload to achieve better iron excretion. However, in early treatment, when there is excess tissue iron, there is some evidence that ascorbic acid may worsen iron toxicity, particularly to the heart. It is therefore recommended that a maximum daily oral dose of 200 mg of ascorbic acid should be used in adults, that vitamin C should not be given within the first month of desferrioxamine treatment or to those with heart failure, and that cardiac function should be monitored during combined use.

Desferrioxamine binds to gallium and may distort gallium-67 imaging results, see Diagnostic Tests, p. 1546.3.

Phenothiazines. Neurological symptoms including loss of consciousness occurred in 2 patients given *prochlorperazine* during desferrioxamine therapy,[1] possibly due to synergistic effects on iron mobilisation. UK licensed product information therefore advises that they should not be used together.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; 56: 345–55.

Pharmacokinetics

Desferrioxamine mesilate is poorly absorbed from the gastrointestinal tract but rapidly absorbed after intramuscular injection or subcutaneous infusion. Peak plasma concentrations occur about 30 minutes after an intramuscular dose. When given parenterally it forms chelates with iron and aluminium ions to form ferrioxamine and aluminoxamine, respectively. The chelates are excreted in the urine and faeces via the bile. Desferrioxamine is metabolised, mainly in the plasma. Elimination of desferrioxamine and ferrioxamine is biphasic after intramuscular injection, with an initial half-life of 1 hour for desferrioxamine and 2.4 hours for ferrioxamine, and a terminal half-life of 6 hours for both compounds. Desferrioxamine is absorbed during peritoneal dialysis if added to the dialysis fluid. It is also removed by dialysis.

References.
1. Allain P, *et al.* Pharmacokinetics and renal elimination of desferrioxamine and ferrioxamine in healthy subjects and patients with haemochromatosis. *Br J Clin Pharmacol* 1987; 24: 207–12.
2. Porter JB. Deferoxamine pharmacokinetics. *Semin Hematol* 2001; 38 (Suppl 1): 63–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Desferal; *Austral.*: Desferal; *Austria*: Desferal; *Belg.*: Desferal; *Braz.*: Desferal; *Canad.*: Desferal; *Chile*: Desferal; *China*: Desferal (得斯芬); *Cz.*: Desferal; *Denm.*: Desferal; Desferin; *Fin.*: Desferal; *Fr.*: Desferal; *Ger.*: Desferal; *Gr.*: Desferal; *Hong Kong*: Desferal; *Hung.*: Desferal; *India*: Desferal; *Indon.*: Desferal; *Irl.*: Desferal; *Israel*: Desferal; *Ital.*: Desferal; *Malaysia*: Desferal; *Mex.*: Desferal; *Neth.*: Desferal; *Norw.*: Desferal; *Philipp.*: Desferal; *Pol.*: Desferal; *Port.*: Desferal; *Rus.*: Desferal (Десферал); *S.Afr.*: Desferal; *Singapore*: Desferal; *Spain*: Desferin; *Swed.*: Desferal; *Switz.*: Desferal; *Thai.*: Desferal; Talifer; *Turk.*: Desferal; *UK*: Desferal; *Ukr.*: Desferal (Десферал); *USA*: Desferal; *Venez.*: Desferal.

Pharmacopoeial Preparations
BP 2014: Desferrioxamine Injection;
USP 36: Deferoxamine Mesylate for Injection.

Dexrazoxane *(BAN, USAN, rINN)*

ADR-529; Deksrazoksan; Dexrazoxano; Dexrazoxanum; ICRF-187; NSC-169780; Дексразоксан.
(+)-(*S*)-4,4′-Propylenebis(piperazine-2,6-dione).
$C_{11}H_{16}N_4O_4$=268.3
CAS — 24584-09-6.
ATC — V03AF02.
ATC Vet — QV03AF02.
UNII — 048L81261F.

Uses and Administration

Dexrazoxane is the *S*-(+)-enantiomer of the antineoplastic drug razoxane and is a cytoprotective agent that is used to reduce the cardiotoxicity of doxorubicin and other anthracyclines (see Effects on the Heart, p. 784.1); it is also used in the management of anthracycline extravasation. Dexrazoxane and its active metabolites chelate iron within the cells and appear to prevent the formation of the anthracycline-iron complex that is thought to be responsible for cardiotoxicity.

Dexrazoxane is used to prevent chronic cumulative cardiomyopathy associated with doxorubicin or epirubicin in patients with advanced or metastatic cancer who have previously received anthracyclines; in many countries use is restricted to adults who have received a minimum cumulative dose of doxorubicin 300 mg/m² or epirubicin 540 mg/m². It is given by intravenous infusion over 15 minutes usually starting about 30 minutes before the anthracycline, as the hydrochloride, although doses are expressed as the base. The dose is calculated on a 10:1 ratio of dexrazoxane to doxorubicin or epirubicin, for instance 500 mg/m² of dexrazoxane is given for every 50 mg/m² of doxorubicin. A reduction in dose may be required in patients with renal impairment (see below).

In patients with anthracycline extravasation, dexrazoxane is given intravenously into a large vein in an area other than that affected by the extravasation. It is given once daily for 3 days, by intravenous infusion over 1 to 2 hours, starting within 6 hours of extravasation; the dose should be given at about the same time each day. The usual dose is 1 g/m² (maximum 2 g) on the first and second days, and 500 mg/m² (maximum 1 g) on the third day.

References.
1. Links M, Lewis C. Chemoprotectants: a review of their clinical pharmacology and therapeutic efficacy. *Drugs* 1999; 57: 293–308.
2. Cvetković RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; 65: 1005–24.
3. Langer SW. Dexrazoxane for anthracycline extravasation. *Expert Rev Anticancer Ther* 2007; 7: 1081–8.
4. Hasinoff BB. The use of dexrazoxane for the prevention of anthracycline extravasation injury. *Expert Opin Invest Drugs* 2008; 17: 217–23.
5. Jones RL. Utility of dexrazoxane for the reduction of anthracycline-induced cardiotoxicity. *Expert Rev Cardiovasc Ther* 2008; 6: 1311–17.
6. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; 27: 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 04/09/09)

Administration in children. Doxorubicin has been used in the treatment of acute lymphoblastic leukaemia in children but cardiotoxicity may be a problem. A randomised study[1] in 206 children found that those given dexrazoxane with doxorubicin had fewer elevations of cardiac troponin T, a marker of myocardial damage, than those given doxorubicin alone, but longer follow-up was needed to assess effects on cardiac function and survival. Longer-term follow-up in this group[2] found that adding dexrazoxane to doxorubicin seemed to have a cardioprotectant effect up to 5 years after treatment, as indicated by ECG measurements of left ventricular structure and function, and this effect was more pronounced in girls than in boys. No adverse effects on relapse risk, frequency of secondary malignancies, or survival were noted. Nonetheless, in June 2011, the EMEA restricted the use of dexrazoxane due to the increased risk of secondary malignancies such as acute myeloid leukaemia and myelodysplastic syndrome (see Carcinogenicity, below), contra-indicating its use in patients under the age of 18 years.

1. Lipshultz SE, *et al.* The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med* 2004; 351: 145–53.
2. Lipshultz SE, *et al.* Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomised, multicentre trial. *Lancet Oncol* 2010; 11: 950–61.

Administration in renal impairment. Dexrazoxane is mainly excreted in the urine and clearance is reduced in patients with renal impairment.[1] Licensed product information recommends a dose reduction of 50% for patients with a creatinine clearance below 40 mL/minute.

1. Brier ME, *et al.* Pharmacokinetics of dexrazoxane in subjects with impaired kidney function. *J Clin Pharmacol* 2011; 51: 731–8.

Adverse Effects and Precautions

Dexrazoxane may add to the bone-marrow depression caused by antineoplastics and frequent complete blood counts are recommended during therapy. At high doses of chemotherapy, where the dexrazoxane dose exceeds 1 g/m², bone-marrow suppression may increase significantly. Leucopenia and thrombocytopenia generally reverse quickly upon stopping dexrazoxane treatment. Anaemia and bone marrow aplasia occur rarely. Although dexrazoxane protects against the cardiotoxic effects of anthracyclines, cardiac function should continue to be monitored when dexrazoxane is used. Other adverse effects reported include gastrointestinal disorders, infection, neurotoxicity, alopecia, fever, pain on injection, and injection site reactions. There may also be an increased risk of thromboembolism when dexrazoxane is given with chemotherapy. Dexrazoxane may increase the urinary clearance of iron and zinc; transient increases in the serum concentrations of triglycerides and amylase can occur, and a transient decrease in serum calcium concentration has been seen.

Dexrazoxane is cytotoxic, and may increase the risk of secondary malignancies when combined with antineoplastic regimens, see Carcinogenicity, below. Teratogenic effects have been seen in *animal* studies, and effective contraception is recommended throughout treatment in both women and men; men should continue with contraceptive measures for at least 3 months after stopping dexrazoxane treatment. There is also some evidence that dexrazoxane may reduce the efficacy of the FAC antineoplastic regimen (fluorouracil, doxorubicin, and cyclophosphamide). Due to the risks associated with dexrazoxane therapy, use in many countries is restricted to adult patients who have received a minimum cumulative dose of doxorubicin 300 mg/m² or epirubicin 540 mg/m².

Liver dysfunction has occasionally occurred in patients treated with dexrazoxane. Patients with known liver function disorders should have their liver function assessed before receiving dexrazoxane for anthracycline extravasation. Clearance of dexrazoxane and its active metabolites may be reduced in patients with renal impairment, see also Administration in Renal Impairment, above.

Carcinogenicity. Dexrazoxane has been associated with an increased incidence of secondary acute myeloid leukaemia or myelodysplastic syndrome in children with Hodgkin's disease or acute lymphoblastic leukaemia (ALL) given dexrazoxane with antineoplastic therapy.[1] Dexrazoxane is the (+)-enantiomer of razoxane, which has also been associated with secondary malignancies, and has topoisomerase II inhibitory activity; it has been suggested the occurrence of secondary malignancies could be attributed to the effect of combining dexrazoxane with multiple antineoplastics, particularly topoisomerase II inhibitors.[2] However, results from studies have been conflicting. Although one study[3] in children with Hodgkin's disease reported an increased incidence of secondary malignancies when dexrazoxane was used with other topoisomerase II inhibitors, it was not designed to assess this effect. An analysis of long-term outcomes of paediatric studies in ALL,[4] included one study in which the 10-year cumulative incidence of secondary malignancies was 4.2% in patients who had received dexrazoxane versus 1.3% in those who had not. However, an analysis of a study[5] in children with leukaemia did not find any association between dexrazoxane and the incidence of secondary malignancies. Nonetheless, the use of dexrazoxane in patients less than 18 years of age is considered contra-indicated in the EU.

1. MHRA. Dexrazoxane: increased risk of secondary malignancies in children with haematological malignancies. *Drug Safety Update* 2010; 4 (2): A1. Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/publication/con093878.pdf (accessed 16/05/11)
2. Novartis UK. Important safety information on Cardioxane (dexrazoxane) (issued 22/07/10). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0907936&RevisionSelectionMethod=Latest (accessed 04/08/10)
3. Tebbi CK, *et al.* Dexrazoxane-associated risk for acute myeloid leukemia/myelodysplastic syndrome and other secondary malignancies in pediatric Hodgkin's disease. *J Clin Oncol* 2007; 25: 493–500.
4. Sabzer WL, *et al.* Long-term results of the pediatric oncology group studies for childhood acute lymphoblastic leukemia 1984-2001: a report from the children's oncology group. *Leukemia* 2010; 24: 355–70.
5. Barry EV, *et al.* Absence of secondary malignant neoplasms in children with high-risk acute lymphoblastic leukemia treated with dexrazoxane. *J Clin Oncol* 2008; 26: 1106–11.

Effects on the skin. Severe cutaneous and subcutaneous necrosis has been reported[1] in a patient who received dexrazoxane by infusion into a peripheral forearm vein, followed by intravenous injection of doxorubicin at a different site in the same arm. Local pain occurred during the dexrazoxane infusion but there was no evidence of extravasation.

1. Lossos IS, Ben-Yehuda D. Cutaneous and subcutaneous necrosis following dexrazoxane-CHOP therapy. *Ann Pharmacother* 1999; 33: 253–4.

Pharmacokinetics

After intravenous infusion dexrazoxane is rapidly distributed mainly in the total body water, with high concentrations in the liver and kidneys; there is no significant entry into the CSF. Plasma protein binding is low (2%). Dexrazoxane undergoes intracellular hydrolysis to active metabolites. Dexrazoxane is mainly excreted in the urine as unchanged drug and metabolites. The elimination half-life is reported to be about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Cardioxane; Savene; *Belg.*: Savene; *Braz.*: Cardioxane; *Canad.*: Zinecard; *Chile*: Cardioxane; *China*: Ao Nuo Xian (奥诺先); *Cz.*: Cardioxane; Cyrdanax; Procard; Savene; *Denm.*: Cardioxane; Savene; *Fin.*: Cardioxane†; *Fr.*: Cardioxane; Savene; *Ger.*: Cardioxane; *Gr.*: Cardioxane; Savene; Zinecard; *Hung.*: Cardioxane; *Irl.*: Cardioxane; Savene; *Israel*: Cardioxane; *Ital.*: Cardioxane; Savene; *Mex.*: Cardioxane; *Neth.*: Cardioxane; Savene; *Norw.*: Savene; *Pol.*: Cardioxane; Savene; *Port.*: Cardioxane; Savene; *Rus.*: Cardioxane (Кардиоксан); *Spain*: Cardioxane; Savene; *Swed.*: Savene; *UK*: Cardioxane; Savene; *USA*: Totect; Zinecard; *Venez.*: Cardioxane.

Dicobalt Edetate *(BAN, rINN)*

Cobalt Edetate; Cobalt EDTA; Cobalt Tetracemate; Dicobalti Edetas; Dicobalto, edetato de; Dikobalt Edetat; Édétate Dicobaltique; Edetato de dicobalto; Edetato dicobaltio; Дикобальта Эдетат.
Cobalt [ethylenediaminetetra-acetato(4-)-*N*,*N*′,*O*,*O*′]cobaltate(II).
$C_{10}H_{12}Co_2N_2O_8$=406.1
CAS — 36499-65-7.
UNII — UKC6GH80QR.

Uses and Administration

Dicobalt edetate is a chelator used in the treatment of severe cyanide poisoning (p. 2156.2). It forms a relatively non-toxic stable ion-complex with cyanide. Owing to its toxicity, dicobalt edetate should be used only in confirmed cyanide poisoning and never as a precautionary measure. A suggested dose is 300 mg given by intravenous injection over about 1 minute, repeated if the response is inadequate; a further dose of 300 mg may be given 5 minutes later if required. For less severe poisoning injections may be given over 5 minutes. Each injection of dicobalt edetate may be followed immediately by 50 mL of glucose 50% intravenously to reduce toxicity. For doses in children, see below.

Administration in children. Although unlicensed in the UK for use in children, the *National Poisons Information Service* suggests an intravenous injection of dicobalt edetate 4 mg/kg given over 1 minute for the treatment of severe cyanide poisoning. This is followed immediately by an intravenous injection of glucose 25%; 25 mL for children aged under 2 years, and 50 mL in those from 2 years.

Adverse Effects, Treatment, and Precautions

Dicobalt edetate may cause vomiting, diarrhoea, and headache. Anaphylactic reactions have occurred and include hypotension, tachycardia, chest pain, urticaria, rash, sweating, and severe facial, laryngeal, and pulmonary oedema. Other reported adverse effects include convulsions and arrhythmias. Hypertonic glucose solution (which appeared to reduce toxicity in early *animal* studies) may be injected after dicobalt edetate for this purpose, see Uses and Administration, above.

The adverse effects of dicobalt edetate are more severe in the absence of cyanide. Therefore, dicobalt edetate should not be given unless cyanide poisoning is confirmed and poisoning is severe such as when consciousness is impaired.

Oedema. A patient with cyanide toxicity developed severe facial and pulmonary oedema after treatment with dicobalt edetate.[1] It has been suggested that when dicobalt edetate is used, facilities for intubation and resuscitation should be immediately available.

1. Dodds C, McKnight C. Cyanide toxicity after immersion and the hazards of dicobalt edetate. *BMJ* 1985; 291: 785–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Kelocyanor; *Gr.*: Kelocyanor.

Digoxin-specific Antibody Fragments

Digoxin Immune Fab (Ovine); F(ab); Fragmentos de anticuerpos específicos antidigoxina; Fragmentos Fab de anticuerpos antidigoxina; Антидигоксин.

ATC — V03AB24.
ATC Vet — QV03AB24.
UNII — YB12NQZ1YN.

Uses and Administration

Digoxin-specific antibody fragments are derived from antibodies produced in sheep immunised to digoxin. Digoxin has greater affinity for the antibodies than for tissue-binding sites, and the digoxin-antibody complex is then excreted in the urine. Digoxin-specific antibody fragments are used to treat severe digoxin or digitoxin intoxication (p. 1355.1) in which conventional treatment is ineffective. Successful treatment of lanatoside C poisoning has also been reported.

It is estimated that 38 or 40 mg (depending on the preparation) of antibody fragments can bind about 500 micrograms of digoxin or digitoxin; the dose is thus calculated using the steady-state plasma concentration or the amount of glycoside ingested. Doses are diluted in sodium chloride 0.9% and given by intravenous infusion over 30 minutes via a 0.22-micrometre in-line filter. If cardiac arrest is imminent the dose may be given as a bolus. In the case of incomplete reversal or recurrence of toxicity a further dose can be given after several hours.

After acute ingestion of an unknown amount of digoxin or digitoxin a dose of 760 or 800 mg is suggested; alternatively an initial dose of 380 or 400 mg can be given with an additional 380 or 400 mg if required. For toxicity during chronic therapy when the steady-state plasma concentration is unknown, a dose of 228 or 240 mg is suggested.

For doses in children, see Administration in Children, below.

Digoxin-specific antibody fragments are being investigated for the treatment of hypertension, particularly in eclampsia and pre-eclampsia.

Administration. It has been suggested[1] that giving digoxin-specific antibody fragments by infusion over 7 hours, after an initial loading dose, could be useful in ensuring adequate antibody concentrations are maintained to bind digoxin as it is released from tissue stores over a prolonged period.

1. Schaumann W, *et al.* Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; 30: 527–33.

Administration in children. Digoxin-specific antibody fragments are licensed in children to treat severe digoxin or digitoxin intoxication in which conventional treatment is ineffective. The dose is calculated using the steady-state plasma concentration or the amount of glycoside ingested, as for adults, see Uses and Administration, above. For acute ingestion of an unknown amount of glycoside, children may also be given the adult dose, although smaller children (20 kg and under) should be individually assessed and monitored for volume overload. For toxicity during chronic therapy when the steady-state plasma concentration is unknown, children weighing over 20 kg may be given the adult dose; for those weighing 20 kg and under a dose of 38 or 40 mg is usually sufficient.

There are reports of successful use in children with cardiac glycoside poisoning.[1,2]

1. Laurent G, *et al.* Anticorps antidigoxine au cours d'une intoxication digitalique sévère chez un nouveau-né de 11 jours. Revue de la littérature. *Ann Cardiol Angeiol (Paris)* 2001; 50: 274–84.
2. Camphausen C, *et al.* Successful treatment of oleander intoxication (cardiac glycosides) with digoxin-specific Fab antibody fragments in a 7-year-old child: case report and review of literature. *Z Kardiol* 2005; 94: 817–23.

Administration in renal impairment. In renal impairment, elimination of antibody-bound digoxin or digitoxin is delayed[1-3] and antibody fragments can be detected in the plasma for 2 to 3 weeks after treatment.[1] The rebound in free-digoxin concentrations that has been reported after treatment with digoxin-specific antibody fragments (see Poisoning, below), occurred much later in patients with renal impairment than in those with normal renal function. Those with severe renal impairment may need to be observed for longer after treatment with antibody fragments, and monitoring of free (unbound) plasma-digoxin concentrations may be useful.[1]

1. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; 27: 1115–33.
2. Allen NM, *et al.* Clinical and pharmacokinetic profiles of digoxin immune Fab in four patients with renal impairment. *DICP Ann Pharmacother* 1991; 25: 1315–20.
3. Ujhelyi MR, *et al.* Disposition of digoxin immune Fab in patients with kidney failure. *Clin Pharmacol Ther* 1993; 54: 388–94.

Poisoning. Digoxin-specific antibody fragments can reverse severe digitalis toxicity with an initial response usually seen within 30 minutes of the end of the infusion. Haemodynamic status normally improves, but in those with heart failure withdrawal of the inotropic support provided by digoxin may produce a decline in cardiac function. Plasma potassium concentrations may fall rapidly after reversal of toxicity. Glycoside toxicity has been reported to recur within 24 hours after treatment with antibody fragments. The reason for this is unclear, although it has been suggested that changes in the distribution of glycoside and antibody fragments may play a role.[1,2] It has been suggested that for either acute or chronic toxicity, half the calculated loading dose (see Uses and Administration, above) should be given initially, with further doses given only if response is inadequate or if toxicity recurs.[3] Digoxin-specific antibody fragments are usually reserved for severe or life-threatening digitalis toxicity, such as that associated with significant hyperkalaemia, arrhythmias, or bradycardia;[3] however they have also been used in patients with less severe toxicity but with poor prognostic features such as underlying cardiac disease or age over 55 years.[4]

Digoxin-specific antibody fragments have also been used to reverse toxicity from cardiac glycosides present in other plants such as common or yellow oleander (p. 2574.3) and in poisoning due to preparations containing toad venom.[5]

1. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; 28: 483–93.
2. Flanagan RJ, Jones AL. Fab antibody fragments: some applications in clinical toxicology. *Drug Safety* 2004; 27: 1115–33.
3. Bateman DN. Digoxin-specific antibody fragments: how much and when? *Toxicol Rev* 2004; 23: 135–43.
4. Lapostolle F, *et al.* Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med* 2008; 36: 3014–18.
5. Brubacher JR, *et al.* Treatment of toad venom poisoning with digoxin-specific Fab fragments. *Chest* 1996; 110: 1282–8.

Adverse Effects and Precautions

Allergic reactions to digoxin-specific antibody fragments have been reported rarely. A pruritic rash, facial flushing and swelling, and chills in the absence of fever have occurred on the day of treatment, and urticaria and thrombocytopenia have been reported up to 16 days after treatment.

Patients known to be allergic to sheep protein and those previously given digoxin-specific antibody fragments may be at greater risk of developing an allergic reaction. An intradermal or skin scratch test may be used to test for sensitivity in those considered to be at high risk.

Blood pressure, ECG, and potassium concentrations should be monitored closely during and after use. Digoxin-specific antibody fragments can interfere with digitalis immunoassay measurements; after treatment, total serum concentrations of digoxin will represent free plus bound digoxin and so can be misleading.

Pregnancy. Although data are scarce, there are reports of the use of digoxin-specific antibody fragments in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Pharmacokinetics

Digoxin-specific antibody fragments bind digoxin to form an inactive complex. These complexes accumulate in the blood before being excreted via the kidneys and the reticuloendothelial system. Digoxin-specific antibody fragments are excreted in the urine with an elimination half-life between 15 and 23 hours. In renal impairment the half-life is increased up to tenfold.

References.
1. Schaumann W, *et al.* Kinetics of the Fab fragments of digoxin antibodies and of bound digoxin in patients with severe digoxin intoxication. *Eur J Clin Pharmacol* 1986; 30: 527–33.
2. Ujhelyi MR, Robert S. Pharmacokinetic aspects of digoxin-specific Fab therapy in the management of digitalis toxicity. *Clin Pharmacokinet* 1995; 28: 483–93.
3. Renard C, *et al.* Pharmacokinetics of digoxin-specific Fab: effects of decreased renal function and age. *Br J Clin Pharmacol* 1997; 44: 135–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Digibind; *Canad.*: Digibind†; DigiFab; *Fr.*: Digibind†; *Gr.*: Digibind; DigiFab; *Hong Kong*: Digitalis Antidote; *UK*: Digibind; DigiFab; *USA*: Digibind†; DigiFab.

Dimercaprol *(BAN, rINN)*

BAL; British Anti-Lewisite; Dimercaprolum; Dimerkaprol; Dimerkaproli; Dimerkaprolis; Димеркапрол.

2,3-Dimercaptopropan-1-ol.

$C_3H_8OS_2$=124.2

CAS — 59-52-9.

ATC — V03AB09.

ATC Vet — QV03AB09.

UNII — 0CPP32S55X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Dimercaprol). A clear colourless or slightly yellow liquid. Soluble in water and in arachis oil; miscible with alcohol and with benzyl benzoate. Store at 2 degrees to 8 degrees in well-filled airtight containers. Protect from light.

USP 36: (Dimercaprol). A colourless or practically colourless liquid, having a disagreeable, mercaptan-like odour. Soluble 1 in 20 of water; soluble in alcohol, in benzyl benzoate, and in methyl alcohol. Store at a temperature not exceeding 8 degrees in airtight containers. Protect from light.

Uses and Administration

Dimercaprol is a chelator that has been used in the treatment of acute poisoning by arsenic (p. 2449.1), gold (p. 131.3), and mercury (p. 2556.3). It may also be used in the treatment of poisoning by other heavy metals such as antimony and bismuth, and, with sodium calcium edetate, in acute lead poisoning (p. 2542.1). However, other chelators may be preferred for systemic use. Dimercaprol has been used in refractory Wilson's disease (p. 1567.3). Dimercaprol 5% has been applied as an ointment for skin lesions or as eye drops for ocular symptoms of arsenic toxicity.

The sulfhydryl groups on dimercaprol compete with endogenous sulfhydryl groups on proteins such as enzymes to combine with these metals; chelation by dimercaprol therefore prevents or reverses any inhibition of the sulfhydryl enzymes by the metal and the dimercaprol-metal complex formed is readily excreted by the kidney. Since the complex may dissociate, particularly at acid pH, or be oxidised, the aim of treatment is to provide an excess of dimercaprol in body fluids until the excretion of the metal is complete.

Dimercaprol should be given by deep intramuscular injection in the treatment of heavy metal poisoning. The individual dose is determined by severity of symptoms and the causative agent. Single doses should not generally exceed 3 mg/kg but single doses of up to 5 mg/kg may be required initially in patients with severe acute poisoning. Various dosage schedules are in use.

In the UK, 400 to 800 mg is given on the first day of treatment, 200 to 400 mg on the second and third days, and 100 to 200 mg on the fourth and subsequent days, all in divided doses. (For a 70-kg adult, this would correspond to a daily dose of about 5.7 to 11.4 mg/kg on the first day.)

Dimercaprol dosage schedules in the USA depend on the causative heavy metal. A recommended regimen for severe *arsenical* or *gold* poisoning is dimercaprol 3 mg/kg given at 4-hourly intervals throughout the first 2 days, 4 times daily on the third day, and then twice daily for 10 days or until recovery. In milder cases, 2.5 mg/kg is given 4 times daily on each of the first 2 days, twice daily on the third day, and then once daily for 10 days. In severe gold dermatitis the *American Hospital Formulary Service* recommends a dose of dimercaprol 2.5 mg/kg every 4 hours for 2 days, then twice daily for about 1 week, and for gold-induced thrombocytopenia, 100 mg of dimercaprol has been given twice daily for 15 days.

For *mercury* poisoning, an initial dose of dimercaprol 5 mg/kg is followed by 2.5 mg/kg one or two times daily for 10 days.

Dimercaprol is also used with sodium calcium edetate (p. 1573.3) for *lead* poisoning, particularly when there are symptoms of lead encephalopathy. Dimercaprol is usually

started first, since sodium calcium edetate may cause mobilisation of stored lead in symptomatic toxicity. A suggested regimen is to give dimercaprol intramuscularly in an initial dose of 4 mg/kg, followed at 4-hourly intervals by dimercaprol 3 to 4 mg/kg intramuscularly and sodium calcium edetate; the sodium calcium edetate may be given either intravenously, or intramuscularly at a different site from the dimercaprol. Treatment may be continued for 2 to 7 days depending on the clinical response; in patients with lead encephalopathy, combined therapy should be continued until the patient is stable. In severe lead poisoning, a minimum of 2 days without treatment should elapse before a second course of therapy with either combined dimercaprol and sodium calcium edetate or sodium calcium edetate alone is considered.

Administration in children. Dimercaprol has been used in children in the treatment of acute poisoning by heavy metals such as arsenic, gold, mercury, antimony, and bismuth. It can also be used with sodium calcium edetate for acute lead poisoning. After the second or third injection of dimercaprol, about 30% of children develop a fever that may persist until treatment is stopped. Doses are the equivalent per unit body-weight to those used in adults, see p. 1549.3. In the UK, the *BNFC* states that the use of dimercaprol in heavy metal poisoning has been superseded by other chelators. However, the *American Hospital Formulary Service* states that infants and children with mercury poisoning have been treated with an intramuscular dose of dimercaprol 3 mg/kg, given every 4 hours for the first 2 days, then every 6 hours for 1 day, then every 12 hours for a further 7 or 8 days.

Adverse Effects and Treatment

The most consistent adverse effects produced by dimercaprol are hypertension and tachycardia. Other adverse effects include nausea, vomiting, headache, burning sensation of the lips, mouth, throat, eyes, and penis, lachrymation and salivation, tingling of the extremities, a sensation of constriction in the throat and chest, muscle pains and muscle spasm, rhinorrhoea, conjunctivitis, sweating, anxiety, weakness, and abdominal pain. Transient reductions in the leucocyte count have also been reported. High doses have produced hypertensive encephalopathy with convulsions and coma. Pain may occur at the injection site and sterile abscesses occasionally develop. In children, fever commonly occurs and persists during therapy.

Adverse effects are dose-related, relatively frequent, and usually reversible. It has been suggested that ephedrine sulfate 30 to 60 mg, given orally 30 minutes before each injection of dimercaprol, may reduce adverse effects; antihistamines may alleviate some of the symptoms.

Precautions

Dimercaprol should be used with care in patients with hypertension or renal impairment. It should be stopped, or continued with extreme caution, if acute renal insufficiency develops during therapy. Alkalinisation of the urine may protect the kidney during therapy by stabilising the dimercaprol-metal complex. Dimercaprol should not be used in patients with hepatic impairment unless due to arsenic poisoning. It should not be used in the treatment of poisoning due to cadmium, iron, or selenium as the dimercaprol-metal complexes formed are more toxic than the metals themselves. Dimercaprol injection is usually formulated in arachis oil, which should be avoided in those with peanut allergy.

G6PD deficiency. Haemolysis has been reported[1] during chelation therapy with dimercaprol and sodium calcium edetate for high blood-lead concentrations in 2 children with a deficiency of G6PD.

1. Janaktraman N, *et al.* Hemolysis during BAL chelation therapy for high blood lead levels in two G6PD deficient children. *Clin Pediatr (Phila)* 1978; 17: 485–7.

Pregnancy. Although data are scarce, there are reports of the use of dimercaprol for poisoning in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; 3: 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Interactions

Iron supplements should not be given during dimercaprol therapy as the dimercaprol-iron complex formed is toxic.

Pharmacokinetics

After intramuscular injection, peak plasma concentrations of dimercaprol occur within 30 to 60 minutes. It is widely distributed but is concentrated in the kidney, liver, and small intestine. Dimercaprol is rapidly metabolised and the metabolites and dimercaprol-metal chelates are excreted in the urine and bile. Elimination is essentially complete within 4 hours of a single dose.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Zorex (Зорекс).

Multi-ingredient Preparations. *Ukr.*: Zorex (Зорекс).

Pharmacopoeial Preparations
BP 2014: Dimercaprol Injection;
USP 36: Dimercaprol Injection.

4-Dimethylaminophenol Hydrochloride

Dimetamfenol Hydrochloride; 4-Dimetilaminofenol, hidrocloruro de; 4-DMAP; 4-Диметиламинофенола Гидрохлорид.

$C_8H_{11}NO,HCl$=173.6

CAS — 619-60-3 (4-dimethylaminophenol); 5882-48-4 (4-dimethylaminophenol hydrochloride).
ATC — V03AB27.
ATC Vet — QV03AB27.
UNII — 0Q0F93G1TR.

Profile

4-Dimethylaminophenol hydrochloride is reported to oxidise haemoglobin to methaemoglobin and has been used with sodium thiosulfate as an alternative to sodium nitrite (p. 1574.3) in the treatment of cyanide poisoning. Doses of 3 to 4 mg/kg have been given intravenously.

References.
1. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)–experimental and clinical overview. *Fundam Appl Toxicol* 1983; 3: 387–96.
2. Weger NP. Treatment of cyanide poisoning with 4-dimethylaminophenol (DMAP)—experimental and clinical overview. *Middle East J Anesthesiol* 1990; 10: 389–412.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: 4-DMAP; *Neth.*: 4-DMAP†.

Diprenorphine Hydrochloride *(BANM, rINNM)*

Diprenorfina, hidrocloruro de; Diprénorphine, Chlorhydrate de; Diprenorphinhydrochlorid; Diprenorphini Hydrochloridum; Hidrocloruro de diprenorfina; M-5050; Дипренорфина Гидрохлорид.

(6*R*,7*R*,14*S*)-17-Cyclopropylmethyl-7,8-dihydro-7-(1-hydroxy-1-methylethyl)-6-*O*-methyl-6,14-ethano-17-normorphine hydrochloride; 2-[(-)-(5*R*,6*R*,7*R*,14*S*)-9a-Cyclopropylmethyl-4,5-epoxy-3-hydroxy-6-methoxy-6,14-ethanomorphinan-7-yl]propan-2-ol hydrochloride.

$C_{25}H_{35}NO_4,HCl$=462.0

CAS — 14357-78-9 (diprenorphine); 16808-86-9 (diprenorphine hydrochloride).
ATC Vet — QV03AB92.
UNII — WBS7IEP4SN.

Pharmacopoeias. In *BP(Vet)*.

BP(Vet) 2014: (Diprenorphine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water; slightly soluble in alcohol; very slightly soluble in chloroform; practically insoluble in ether. A 2% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Diprenorphine hydrochloride is an opioid antagonist used as a radioligand in positron-emission tomography to image opiate receptors. It is also used in veterinary medicine to reverse the effects of etorphine hydrochloride.

Ditiocarb Sodium *(rINN)*

DDC; DDTC; DEDC; DeDTC; Dithiocarb Sodium; Ditiocarbe Sodique; Ditiocarbo sódico; Ditiocarbum Natricum; DTC; Sodium Diethyldithiocarbamate; Sodu dietyloditiokarbaminian; U-14624; Дитиокарб Натрий.

$C_5H_{10}NNaS_2$=171.3

CAS — 148-18-5.
UNII — A5304YEB5E.

NOTE. The code DDC has also been used as a synonym for Zalcitabine, p. 1023.2.

Profile

Ditiocarb sodium is a chelator that has been used in nickel carbonyl poisoning. Disulfiram (p. 2495.3), which is rapidly metabolised to ditiocarb, has been used as an alternative. Ditiocarb has also been used in the destruction of cisplatin wastes (see Handling and Disposal, p. 768.2).

Edetic Acid *(BAN, rINN)*

Acide Édétique; Ácido edético; Ácido etilendiaminotetraacético; Acido Etilendiamminotetraacetico; Acidum Edeticum; Edathamil; Edético, ácido; Edetiinihappo; Edetinsäure; Edetinsyra; Edeto rūgštis; EDTA; Ethyleendiaminetetra-azijnzuur; Ethylendiamintetraessigsäure; Etiléndiamintetraecetsav; Etilén-diamin-tetraecetsav; Kwas edetynowy; Kyselina edetová; Tetracemic Acid; Эдетовая Кислота.

Ethylenediaminetetra-acetic acid.

$C_{10}H_{16}N_2O_8$=292.2

CAS — 60-00-4.
UNII — 9G34HU7RV0.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Edetic Acid). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water and in alcohol. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Edetic Acid). A white crystalline powder. Very slightly soluble in water; soluble in solutions of alkali hydroxides.

Sodium Edetate

Monosodium Edetate; Sodu edetynian; Эдетат Натрия.

CAS — 17421-79-3 (monosodium edetate).
ATC — S01XA05.
ATC Vet — QS01XA05.

NOTE. The name sodium edetate has been used in the literature for various sodium salts of edetic acid. Do not confuse with sodium calcium edetate (p. 1573.2) or etomidate (p. 1901.1); see also Inappropriate Administration, p. 1551.2.

Disodium Edetate *(BAN)*

Dinatrii Edetas; Dinatrii Edetas Dihydricus; Dinatrio edetatas; Dinatriumedetaatti; Dinatriumedetat; Disodium Edathamil; Disodium EDTA; Disodium Tetracemate; Disodu edetynian; Edetan disodný dihydrát; Édétate disodique; Edetate Disodium; Edetato disódico; Edetynian disodu; EDTA disódico; Natrii Edetas; Natriumedetat; Nátrium-edetát; Sodium Versenate.

Disodium dihydrogen ethylenediaminetetra-acetate dihydrate.

$C_{10}H_{14}N_2Na_2O_8.2H_2O$=372.2

CAS — 139-33-3 (anhydrous disodium edetate); 6381-92-6 (disodium edetate dihydrate).
ATC — S01XA05.
ATC Vet — QS01XA05.
UNII — 8NLQ36F6MM (anhydrous disodium edetate); 7FLD91C86K (disodium edetate dihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Disodium Edetate). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.0 to 5.5. Protect from light.

USP 36: (Edetate Disodium). A white crystalline powder. Soluble in water. pH of a 5% solution in water is between 4.0 and 6.0.

Trisodium Edetate

Edetate Trisodium (USAN); Edetato trisódico.

Trisodium hydrogen ethylenediaminetetra-acetate.

$C_{10}H_{13}N_2Na_3O_8$=358.2

CAS — 150-38-9.
ATC — S01XA05.
ATC Vet — QS01XA05.
UNII — 420IP921MB.

Tetrasodium Edetate

Edetate Sodium (USAN).

$C_{10}H_{12}N_2Na_4O_8$=380.2

CAS — 64-02-8.
ATC — S01XA05.
ATC Vet — QS01XA05.
UNII — MP1J8420LU.

Incompatibility. Edetic acid and its salts chelate bivalent and trivalent metals and may affect the activity of drugs

such as zinc insulin that contain such ions. Additives stabilised with disodium edetate may chelate trace metals in TPN solutions. Although edetates may enhance the antimicrobial efficacy of some disinfectants (see Chloroxylenol, p. 1748.2), other preservatives may be inactivated. For reference to the inactivation of phenylmercuric salts by disodium edetate, see Incompatibility, under Phenylmercuric Nitrate, p. 1765.2. For a report of edetates reducing the antimicrobial efficacy of thiomersal, see Incompatibility, p. 1771.3.

Uses and Administration

Edetic acid and its salts are chelators; sodium edetate has a high affinity for calcium, with which it forms a stable, soluble complex that is readily excreted by the kidneys. It is given intravenously in the emergency treatment of hypercalcaemia (p. 1776.1). It has also been used to control digitalis-induced cardiac arrhythmias, although less toxic agents are generally preferred (p. 1355.1). It has also been applied topically to the eyes as a collagenase inhibitor or to treat calcium deposits such as in band keratopathy or after calcium hydroxide burns.

Sodium edetate also chelates other polyvalent metals but, unlike sodium calcium edetate, which is saturated with calcium, it is not used for the treatment of heavy metal poisoning since hypocalcaemia rapidly develops.

In the treatment of hypercalcaemia, injections containing varying amounts of disodium edetate are used, diluted with 500 mL of sodium chloride 0.9% or glucose 5% and infused over at least 3 hours. A daily dose of 50 mg/kg up to a maximum of 3 g may be given for 5 days; repeated if necessary after 2 drug-free days, up to a total of 15 doses. However, it is generally recommended that other measures to lower calcium concentrations should also be used, and disodium edetate therapy restricted to 48 hours. The trisodium salt has also been used.

Edetates are also used in pharmaceutical manufacturing as well as having other industrial applications and as anticoagulants for blood taken for haematological investigations. Sodium edetates are used in cleaners for contact lenses and as antoxidant synergists in cosmetic and pharmaceutical preparations. Other salts of edetic acid that are used clinically include sodium calcium edetate (p. 1573.2), dicobalt edetate (p. 1548.3), and sodium feredetate (p. 2088.3).

Atherosclerosis. Calcium is thought to be necessary for several steps in atherogenesis and removal of calcium from atherosclerotic plaques using a chelator such as disodium edetate has been tried in patients with atherosclerosis (p. 1250.2). However, reports of beneficial clinical responses are largely anecdotal or from small, short-term, or uncontrolled clinical studies; a meta-analysis[1] of controlled studies concluded that there was insufficient evidence of benefit or harm, and a further randomised study[2] in patients with coronary heart disease found no benefit with sodium edetate treatment. In addition, adverse effects are common with chelation therapy, and fatalities have been reported;[3] literature reviews[4,5] considering both uncontrolled and controlled studies have concluded that in view of the potential toxicity of such treatment it should be considered obsolete.

1. Dans AL, *et al.* Chelation therapy for atherosclerotic cardiovascular disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 04/10/05).
2. Knudtson ML, *et al.* Chelation therapy for ischemic heart disease: a randomized controlled trial. *JAMA* 2002; **287:** 481–6.
3. Magee R. Chelation treatment of atherosclerosis. *Med J Aust* 1985; **142:** 514–15.
4. Ernst E. Chelation therapy for peripheral arterial occlusive disease: a systematic review. *Circulation* 1997; **96:** 1031–3.
5. Ernst E. Chelation therapy for coronary heart disease: an overview of all clinical investigations. *Am Heart J* 2000; **140:** 139–41.

Gallstones. Edetic acid has been suggested as a possible solvent for non-cholesterol gallstones (p. 2639.1).

Adverse Effects and Treatment

Edetic acid, used as a pharmaceutical excipient, is generally well tolerated. It chelates calcium, and hypocalcaemia has occurred with prolonged use or rapid infusion; when included in preparations for the mouth, calcium may be leached from the teeth. Adverse effects have been reported after inhalation of solutions containing edetic acid, and when used as an excipient in topical formulations, it has rarely caused skin sensitisation.

With sodium edetate, adverse effects are similar to Sodium Calcium Edetate, p. 1574.1. Sodium edetate may also cause hypokalaemia or hypomagnesaemia, and blood glucose concentrations may be reduced. Rapid intravenous infusion or high serum concentrations of sodium edetate may cause a sudden drop in serum-calcium concentrations, and tetany, convulsions, respiratory arrest, and cardiac arrhythmias may result. Calcium supplements may be given intravenously for hypocalcaemia but should be used with extreme caution in patients with tetany, particularly in digitalised patients since the effect of the digitalis may be reversed.

References.

1. Morgan BW, *et al.* Adverse effects in 5 patients receiving EDTA at an outpatient chelation clinic. *Vet Hum Toxicol* 2002; **44:** 274–6.
2. Prabhu A, *et al.* Chelation therapy for coronary heart disease. *Am Heart J* 2002; **144:** E10.

Effects on the respiratory tract. Inhalation of an ipratropium nebuliser solution that contained edetic acid as one of the preservatives caused bronchoconstriction in 6 of 22 patients with asthma.[1] Inhalation of edetic acid alone produced dose-related bronchoconstriction that persisted for more than 1 hour.

1. Beasley CRW, *et al.* Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ* 1987; **294:** 1197–8.

Inappropriate administration. There have been fatalities in both children and adults when they were given sodium edetate instead of *sodium calcium edetate* (p. 1573.2), which is a chelator used for the treatment of lead poisoning.[1,2] The FDA had received reports[3] of 11 deaths associated with the use of sodium edetate over the period 1971 to 2007; in 5 cases, sodium edetate was given instead of sodium calcium edetate, and in 2 cases, sodium edetate was given instead of *etomidate* (p. 1901.1). In some cases, confusion had arisen due to the use of the term EDTA in prescribing the drug. The FDA recommended that the full product name be used, and that prescribers should consider including the indication for use on the prescription.[2] Subsequently, sodium edetate products were withdrawn in the USA.

1. CDC. Deaths associated with hypocalcemia from chelation therapy—Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR* 2006; **55:** 204–7. Also available at: http://www.cdc.gov/mmwr/PDF/wk/mm5508.pdf (accessed 12/08/10)
2. FDA Public Health Advisory. Edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051138.htm (accessed 12/08/10)
3. FDA. Questions and answers on edetate disodium (marketed as Endrate and generic products) (issued 16th January 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm113738.htm (accessed 12/08/10)

Precautions

Sodium edetate should be used with caution, if at all, in patients with renal impairment or anuria. Caution is also required in patients with hypocalcaemia, hypokalaemia, tuberculosis, impaired cardiac function, diabetes mellitus, or a history of seizures. Renal, hepatic, and cardiac function should be monitored regularly, along with blood pressure and serum and urinary electrolytes, particularly calcium, magnesium, and potassium; daily urinalysis is also recommended. Sodium edetate is irritant to the tissues and must be diluted before infusion; the recommended rate should not be exceeded. There may be an increased risk of nephrotoxicity when using sodium edetate to treat hypercalcaemia associated with metastatic bone disease.

Interference with laboratory tests. Disodium edetate may interfere with serum-calcium determination using the oxalate method giving lower concentrations than expected. Sampling just before the next dose or acidifying the sample will minimise the effect.

BLOOD TESTING. Pseudothrombocytopenia due to platelet clumping is a recognised complication of the use of edetates as anticoagulants for blood sampling and may lead to diagnostic errors.[1] The mechanism appears to be antibody-mediated. Alternative anticoagulants have been suggested.[1,2]

1. Bizzaro N. EDTA-dependent pseudothrombocytopenia: a clinical and epidemiological study of 112 cases, with 10-year follow-up. *Am J Hematol* 1995; **50:** 103–9.
2. Lippi U, *et al.* EDTA-induced platelet aggregation can be avoided by a new anticoagulant also suitable for automated complete blood count. *Haematologica* 1990; **75:** 38–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Chelatran†; *Irl.*: Limclair†; *Venez.*: Edetil.

Multi-ingredient Preparations. *Canad.*: Largal Ultra; Mylan-Eti-Cal; *Ger.*: Urgosan; *India*: Fairgenol-H; *Israel*: Claritone; *Mex.*: Adapettes; *UK*: Uriflex G; Uriflex R; *USA*: Clear Eyes Contact Lens Relief; Summer's Eve Post-Menstrual; Triv; Zonite.

Pharmacopoeial Preparations

BP 2014: Disodium Edetate Eye Drops; Trisodium Edetate Infusion;
USP 36: Edetate Disodium Injection.

Ferric Citrate

Ferrum Citricum Oxidatum; Ferrum Citricum Oxydatum; KRX-0502.

CAS — 2338-05-8; 28633-45-6; 3522-50-7.
ATC — B03AB06.
ATC Vet — QB03AB06.
UNII — 63G354M39Z.

NOTE. The name Zerenex has been used as a trade mark for ferric citrate.

Profile

Ferric citrate is an oral, iron-based compound that binds to phosphate to form a non-absorbable complex. It is under investigation for the treatment of hyperphosphataemia in patients with end-stage renal disease.

Homoeopathy

Ferric citrate is used in homoeopathic medicines under the following names: Citrate ferrique; Ferric citrate; Ferrum cit; Ferrum citricum.

Flumazenil *(BAN, USAN, rINN)*

Flumatsenilli; Flumazénil; Flumazenilis; Flumazenilo; Flumazenilum; Flumazepil; Ro-15-1788; Ro-15-1788/000; Флумазенил.

Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine-3-carboxylate.

$C_{15}H_{14}FN_3O_3$=303.3

CAS — 78755-81-4.
ATC — V03AB25.
ATC Vet — QV03AB25.
UNII — 40P7XK9392.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Flumazenil). A white or almost white crystalline powder. Very slightly soluble in water; freely soluble in dichloromethane; sparingly soluble in methyl alcohol.

USP 36: (Flumazenil). A white to off-white powder. Practically insoluble in water; slightly soluble in acidic aqueous solutions. Store in airtight containers.

Uses and Administration

Flumazenil is a benzodiazepine antagonist that acts competitively at CNS benzodiazepine receptors. It is used in anaesthesia and intensive care to reverse benzodiazepine-induced sedation; it may also be used to treat benzodiazepine overdosage (but see warnings in Precautions, p. 1552.3, and under Benzodiazepine Antagonism: Overdosage, p. 1552.1).

Flumazenil should be given by slow intravenous injection or infusion. Reversal of benzodiazepine-induced sedation usually starts within 1 to 2 minutes of the end of the injection, with the peak effect occurring after 6 to 10 minutes.

The usual initial dose for the **reversal of benzodiazepine-induced sedation** is 200 micrograms, followed at intervals of 60 seconds by further doses of 100 to 200 micrograms if required, to a maximum total dose of 1 mg or occasionally 2 mg (usual range, 0.3 to 1 mg); each dose should be given over 15 seconds, and further doses should only be given if an adequate response has not occurred 45 seconds after completion of the injection. If drowsiness recurs an intravenous infusion may be used, at a rate of 100 to 400 micrograms/hour, adjusted according to response. Alternatively, further doses of up to 1 mg, in boluses of 200 micrograms as above, may be given at 20-minute intervals to a maximum of 3 mg in one hour. Patients at risk from the effects of benzodiazepine reversal, such as those dependent on benzodiazepines, should receive smaller bolus injections of 100 micrograms. For doses in children, see p. 1552.1.

The usual initial dose for the management of **benzodiazepine overdose** is 200 micrograms given intravenously over 30 seconds. A further dose of 300 micrograms can be given after another 30 seconds and can be followed by doses of 500 micrograms at one-minute intervals if required, to a total dose of 3 mg or occasionally 5 mg. If a dose of up to 5 mg produces no response then further doses are unlikely to be effective. If symptoms of intoxication recur, repeated doses may be given at 20-minute intervals; not more than 1 mg, in boluses of 500 micrograms as above, should be given at any one time and not more than 3 mg in one hour. Alternatively, an intravenous infusion may be given at a usual rate of 100 to 500 micrograms/hour and adjusted according to response.

If signs of overstimulation occur during the use of flumazenil, then diazepam or midazolam may be given by slow intravenous injection.

Flumazenil labelled with carbon-11 (p. 2223.1) has been used for studying GABA receptors by positron emission tomography.

Flumazenil is being investigated for hypersomnia, obsessive-compulsive disorder, and alcobol dependence.

General references.

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; 42: 1061–89.
2. Hoffman RJ, Warren EW. Flumazenil: a benzodiazepine antagonist. *Clin Pharm* 1993; 12: 641–56.
3. Krenzelok EP. Judicious use of flumazenil. *Clin Pharm* 1993; 12: 691–2.
4. Seger DL. Flumazenil—treatment or toxin. *J Toxicol Clin Toxicol* 2004; 42: 209–16.

Administration. Flumazenil is usually used intravenously, but has also been given by intramuscular injection,[1] orally,[1,2] rectally,[1] and via an endotracheal tube.[3] Intranasal administration has been found to be effective in children.[1,4,5]

1. McGlone R, *et al.* A comparison of intramuscular ketamine with high dose intramuscular midazolam with and without intranasal flumazenil in children before suturing. *Emerg Med J* 2001; 18: 34–8.
2. Girdler NM, *et al.* A randomised, controlled trial of cognitive and psychomotor recovery from midazolam sedation following reversal with oral flumazenil. *Anaesthesia* 2002; 57: 868–76.
3. Palmer RB, *et al.* Endotracheal flumazenil: a new route of administration for benzodiazepine antagonism. *Am J Emerg Med* 1998; 16: 170–2.
4. Heard C, *et al.* Intranasal flumazenil and naloxone to reverse oversedation in a child undergoing dental restorations. *Paediatr Anaesth* 2009; 19: 795–7.
5. Scheepers LD, *et al.* Plasma concentration of flumazenil following intranasal administration in children. *Can J Anaesth* 2000; 47: 120–4.

Administration in children. In children, flumazenil is used to reverse benzodiazepine-induced sedation. UK and US licensed product information recommend initial doses of flumazenil 10 micrograms/kg (maximum single dose 200 micrograms) by intravenous injection over 15 seconds to reverse the effects of benzodiazepines given for conscious sedation in children from 1 to 17 years of age. If necessary this can be repeated 45 seconds after completion of the previous injection, up to a maximum of 4 additional times to a total dose of 50 micrograms/kg or 1 mg, whichever is lower. The *BNFC* suggests that this dose may also be used to reverse the sedative effects of benzodiazepines in neonates and children under 12 months of age. If drowsiness recurs after the initial injection the *BNFC* recommends giving subsequent flumazenil doses by intravenous infusion. Neonates and children up to 18 years of age may be given 2 to 10 micrograms/kg per hour (to a maximum of 400 micrograms/hour in those aged 1 month and over), adjusted according to response.

Although flumazenil is not licensed in the UK for benzodiazepine overdose in children, it may be useful in those who are naive to benzodiazepines, or for preventing the need for ventilation, particularly in children with severe respiratory disorders. The *National Poisons Information Service* suggests an initial dose of 10 micrograms/kg given by intravenous injection over 30 seconds in children over 4 years of age. This can be repeated once if required, 30 seconds after completion of the initial injection; no more than 2 doses may be given in 24 hours. Alternatively, an intravenous infusion of 10 micrograms/kg per hour may be used.

Benzodiazepine antagonism. Flumazenil is a specific benzodiazepine antagonist that binds competitively with benzodiazepine receptors, reversing the centrally mediated effects of benzodiazepines. Its effects are evident within a few minutes of intravenous injection, even after substantial doses of benzodiazepines, and last for up to 3 hours depending on the dose and on the characteristics of the benzodiazepine intoxication. In patients who have taken benzodiazepines for prolonged periods, flumazenil may precipitate withdrawal symptoms.

SEDATION. Flumazenil reduces sedation and amnesia after the use of benzodiazepines for induction or maintenance of general anaesthesia, and in patients undergoing minor surgery or diagnostic procedures who are given benzodiazepines for conscious sedation.[1] Sedation may recur, particularly if long-acting benzodiazepines have been used, and there have been reports of increased analgesic requirements and anxiety after use of flumazenil. Although flumazenil may antagonise the obvious effects of sedation, higher cognitive functions may still be impaired[2,3] and the patient may be unfit to be discharged unless accompanied. Although experience with flumazenil in children is limited, it appears to be well tolerated and effective when used to reverse conscious sedation.[4] Flumazenil has also been used in intensive care to reverse sedation and assist in weaning from mechanical ventilation, but is not routinely recommended.

OVERDOSAGE. Flumazenil may be used as an adjunct in the management of benzodiazepine overdose including overdose involving multiple agents. However, its use may unmask the effects of other intoxicants,[5] and since benzodiazepine overdose is rarely lethal and may even protect against the toxicity of other drugs,[6] flumazenil is not recommended in mixed overdose,[7] particularly when involving tricyclic antidepressants. Repeated doses of flumazenil may be needed to maintain consciousness depending on the benzodiazepine responsible and the magnitude of the overdose; continuous infusion has also been used.[8,9]

1. Brogden RN, Goa KL. Flumazenil: a reappraisal of its pharmacological properties and therapeutic efficacy as a benzodiazepine antagonist. *Drugs* 1991; 42: 1061–89.
2. Sanders LD, *et al.* Reversal of benzodiazepine sedation with the antagonist flumazenil. *Br J Anaesth* 1991; 66: 445–53.
3. Girdler NM, *et al.* A randomised crossover trial of post-operative cognitive and psychomotor recovery from benzodiazepine sedation: effects of reversal with flumazenil over a prolonged recovery period. *Br Dent J* 2002; 192: 335–9.
4. Shannon M, *et al.* Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. *J Pediatr* 1997; 131: 582–6.
5. Weinbroum AA, *et al.* A risk-benefit assessment of flumazenil in the management of benzodiazepine overdose. *Drug Safety* 1997; 17: 181–96.
6. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness: controversies in the use of a 'coma cocktail'. *JAMA* 1995; 274: 562–9.
7. Carvalho C, Walker DA. Coma cocktail: a role for flumazenil? *Br J Hosp Med* 2007; 68: 112.
8. Brammer G, *et al.* Continuous intravenous flumazenil infusion for benzodiazepine poisoning. *Vet Hum Toxicol* 2000; 42: 280–1.
9. Chern C-H, *et al.* Continuous flumazenil infusion in preventing complications arising from severe benzodiazepine intoxication. *Am J Emerg Med* 1998; 16: 238–41.

Hepatic encephalopathy. Flumazenil has been tried in hepatic encephalopathy (p. 1808.2) because of the suspected role of benzodiazepine-like agonists in the pathogenesis of the disorder.[1,2] However, benefits have generally been modest, and a meta-analysis[3] concluded that flumazenil did produce short-term improvement of hepatic encephalopathy but had no effect on recovery or survival; it might be considered for patients with chronic liver disease and hepatic encephalopathy but routine clinical use was not recommended.

1. Grimm G, *et al.* Improvement of hepatic encephalopathy treated with flumazenil. *Lancet* 1988; ii: 1392–4.
2. Basile AS, *et al.* The pathogenesis and treatment of hepatic encephalopathy: evidence for the involvement of benzodiazepine receptor ligands. *Pharmacol Rev* 1991; 43: 27–71.
3. Als-Nielsen B, *et al.* Benzodiazepine receptor antagonists for hepatic encephalopathy. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 04/10/05).

Non-benzodiazepine antagonism. Although flumazenil is a specific benzodiazepine antagonist, it may also block the effects of other drugs that act via the benzodiazepine receptor. In a double-blind study[1] in healthy subjects, flumazenil rapidly antagonised clinical sedation induced by zolpidem, and a rapid response to flumazenil has been reported[2] in a patient who presented in a coma following mixed overdosage with zolpidem, alcohol, and prothipendyl (although use of flumazenil in mixed overdosage is generally contra-indicated). A retrospective analysis[3] similarly noted recovery in 17 of 20 patients with zopiclone overdose who were treated with flumazenil. Flumazenil has also been tried in zaleplon toxicity.[4] Although unlicensed in the UK, the *National Poisons Information Service* suggests that flumazenil can be used to treat severe toxicity from other sedatives that act via the benzodiazepine receptor such as zolpidem, zopiclone, and zaleplon; it is rarely required but may be useful in children who are naive to benzodiazepines, or for preventing the need for ventilation, particularly in those with severe respiratory disorders. It is given in the same doses as those used for benzodiazepine overdose, see Uses, p. 1551.3.

There have also been reports of flumazenil reversing coma associated with antihistamines,[5,6] carisoprodol,[7] and gabapentin.[8] Several other drugs are reported[7] to be reversed by flumazenil including baclofen, cannabis, carbamazepine, cloral hydrate, chlorzoxazone, and meprobamate; however, efficacy has not been established. Although reversal of alcohol-induced sedation has also been suggested, a controlled study[9] found no effect with flumazenil at a dose comparable to that used for benzodiazepine overdosage.

1. Patat A, *et al.* Flumazenil antagonizes the central effects of zolpidem, an imidazopyridine hypnotic. *Clin Pharmacol Ther* 1994; 56: 430–6.
2. Lheureux P, *et al.* Zolpidem intoxication mimicking narcotic overdose: response to flumazenil. *Hum Exp Toxicol* 1990; 9: 105–7.
3. Yang C-C, Deng J-F. Utility of flumazenil in zopiclone overdose. *Clin Toxicol* 2008; 46: 920–1.
4. Höjer J, *et al.* Zaleplon-induced coma and bluish-green urine: possible antidotal effect by flumazenil. *J Toxicol Clin Toxicol* 2002; 40: 571–2.
5. Lassaletta A, *et al.* Reversal of an antihistamine-induced coma with flumazenil. *Pediatr Emerg Care* 2004; 20: 319–20.
6. Plant JR, MacLeod DB. Response of a promethazine-induced coma to flumazenil. *Ann Emerg Med* 1994; 24: 979–82.
7. Roberge RJ, *et al.* Flumazenil reversal of carisoprodol (Soma) intoxication. *J Emerg Med* 2000; 18: 61–4.
8. Butler TC, *et al.* Flumazenil and dialysis for gabapentin-induced coma. *Ann Pharmacother* 2003; 37: 74–6.
9. Lheureux P, Askenasi R. Efficacy of flumazenil in acute alcohol intoxication: double blind placebo-controlled evaluation. *Hum Exp Toxicol* 1991; 10: 235–9.

Adverse Effects and Precautions

Adverse effects after use of flumazenil may be due to the reversal of benzodiazepine effects or benzodiazepine withdrawal syndrome (p. 1065.1). Adverse effects most frequently reported with flumazenil alone are dizziness, increased sweating, pain at injection site, headache, and abnormal or blurred vision. Nausea, vomiting, fatigue, cutaneous vasodilatation, dry mouth, tremor, chills, dyspnoea, cough, nasal congestion, hiccups, and injection site reactions such as thrombophlebitis and rash have occurred. Hypersensitivity reactions including anaphylaxis have been seen. Palpitations have been reported after rapid injection; other cardiovascular adverse effects include tachycardia or bradycardia, extrasystole, hypotension or hypertension, and chest pain.

Anxiety, fear, agitation, and emotional lability have occurred with flumazenil, and care is required in patients with a history of anxiety or panic attacks. Other nervous system adverse effects include confusion, drowsiness or insomnia, and paraesthesia. Seizures have occurred, particularly in patients with epilepsy or severe hepatic impairment, or those who have been taking benzodiazepines for long-term sedation. Eye disorders include visual field defects, diplopia, strabismus, increased lachrymation, and ear disorders include transient hearing impairment, hyperacusis, and tinnitus. Speech disorders include dysphonia. Patients who have taken benzodiazepines for prolonged periods are particularly at risk of developing withdrawal symptoms and rapid injection of flumazenil should be avoided in such patients. Flumazenil should not be used to treat benzodiazepine dependence or benzodiazepine withdrawal syndrome, and caution is required in patients with other drug dependencies.

Because of its short duration of action, patients given flumazenil to reverse benzodiazepine-induced sedation should be kept under close observation; further doses of flumazenil may be necessary. Flumazenil is contra-indicated in patients who are receiving benzodiazepines to control potentially life-threatening conditions and should not be given to epileptic patients who have been receiving benzodiazepines for a prolonged period to control seizures. Use after cardiac arrest is also contra-indicated.

In cases of mixed overdose, flumazenil may unmask adverse effects of other psychoactive drugs. In particular, it should not be used in the presence of severe intoxication with tricyclic and related antidepressants as convulsions, arrhythmias, and cardiac arrest can be precipitated.

Flumazenil should not be given to patients who have received neuromuscular blockers until the effects of neuromuscular blockade have fully cleared. Dosage should be adjusted individually; in high-risk or anxious patients, and after major surgery, it may be preferable to maintain some sedation during the early postoperative period. Flumazenil should be used with caution in patients with head injury since it may precipitate seizures or alter cerebral blood flow and increase intracranial pressure.

Careful titration of dosage is recommended in hepatic impairment.

Cardiac arrhythmias,[1] sometimes preceded by tonic-clonic (grand mal) seizures[2,3] and occasionally fatal,[2] have been reported in several patients after the use of flumazenil for mixed overdoses with benzodiazepines and other psychotropics. Heart block has also been reported[4] after flumazenil use in a patient who had taken benzodiazepines, paracetamol, nifedipine, and atenolol. Death from refractory tonic-clonic seizures has been reported in a patient[5] after the use of flumazenil for a mixed overdose with a benzodiazepine and a tricyclic antidepressant.

Death from respiratory failure occurred in an 83-year-old woman after sedation with midazolam[6] despite use of flumazenil, although some[7] considered that this did not represent a failure by flumazenil to reverse the depressive effects on respiration of midazolam. Ventricular fibrillation followed by asystole and death has been reported in a patient given flumazenil during weaning from assisted ventilation (a period during which diazepam had been given).[8]

1. Short TG, *et al.* Ventricular arrhythmia precipitated by flumazenil. *BMJ* 1988; 296: 1070–1.
2. Burr W, *et al.* Death after flumazenil. *BMJ* 1989; 298: 1713.
3. Marchant B, *et al.* Flumazenil causing convulsions and ventricular tachycardia. *BMJ* 1989; 299: 860.
4. Herd B, Clarke F. Complete heart block after flumazenil. *Hum Exp Toxicol* 1991; 10: 289.
5. Haverkos GP, *et al.* Fatal seizures after flumazenil administration in a patient with mixed overdose. *Ann Pharmacother* 1994; 28: 1347–9.
6. Lim AG. Death after flumazenil. *BMJ* 1989; 299: 858–9. Correction. *ibid.*: 1531.
7. Birch BRP, Miller RA. Death after flumazenil? *BMJ* 1990; 300: 467–8.
8. Katz Y, *et al.* Cardiac arrest associated with flumazenil. *BMJ* 1992; 304: 1415.

Effects on mental function. Although flumazenil is considered to lack agonist properties, a study[1] in healthy subjects found that intravenous flumazenil resulted in impairment of some measures of cognition and alertness. A severe

acute psychotic disorder, which developed during treatment with flumazenil in a patient with hepatic encephalopathy, resolved when flumazenil was discontinued.[2]

1. Neave N, *et al.* Dose-dependent effects of flumazenil on cognition, mood, and cardio-respiratory physiology in healthy volunteers. *Br Dent J* 2000; 189: 668–74.
2. Seebach J, Jost R. Flumazenil-induced psychotic disorder in hepatic encephalopathy. *Lancet* 1992; 339: 488–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies flumazenil as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. Although data are scarce, there are reports of the use of flumazenil in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Pharmacokinetics

Flumazenil is absorbed from the gastrointestinal tract but undergoes extensive first-pass hepatic metabolism and has a systemic bioavailability of about 20%. It is about 50% bound to plasma proteins, mostly albumin. It is metabolised in the liver, mainly to the inactive carboxylic acid form. Intake of food during an intravenous infusion results in a 50% increase in clearance, probably due to the postprandial increase in liver perfusion. Flumazenil is excreted as metabolites, mainly in the urine, with a small amount in the faeces. The terminal elimination half-life is about 40 to 80 minutes. In patients with hepatic impairment the clearance of flumazenil is decreased with a resultant increase in half-life.

References.

1. Klotz U, *et al.* Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *Eur J Clin Pharmacol* 1984; 27: 115–17.
2. Roncari G, *et al.* Pharmacokinetics of the new benzodiazepine antagonist Ro 15-1788 in man following intravenous and oral administration. *Br J Clin Pharmacol* 1986; 22: 421–8.
3. Breimer LTM, *et al.* Pharmacokinetics and EEG effects of flumazenil in volunteers. *Clin Pharmacokinet* 1991; 20: 491–6.
4. Jones RDM, *et al.* Pharmacokinetics of flumazenil and midazolam. *Br J Anaesth* 1993; 70: 286–92.
5. Roncari G, *et al.* Flumazenil kinetics in the elderly. *Eur J Clin Pharmacol* 1993; 45: 585–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fadaflumaz; Flumage; Flumanovag; Flumazen; Fluxifarm†; *Austral.*: Anexate; *Austria*: Anexate; *Belg.*: Anexate; *Braz.*: Flumazen; Flumazil; Flunexil; Lanexat; *Canad.*: Anexate†; *Chile*: Fluoxem; Lanexat; *China*: Anexate (安易行); Lai Yi (莱意); *Cz.*: Anexate; *Fin.*: Lanexat†; *Fr.*: Anexate; *Ger.*: Anexate; *Gr.*: Anexate; Demoxate; Flumexate; *Hong Kong*: Anexate; *Hung.*: Anexate; *Indon.*: Anexate†; *Irl.*: Anexate; *Israel*: Anexate; *Ital.*: Anexate; *Malaysia*: Anexate; Antabenz; *Mex.*: Lanexat; *Neth.*: Anexate; *Norw.*: Anexate; *NZ*: Anexate; *Philipp.*: Anexate; *Pol.*: Anexate; *Port.*: Anexate; *Rus.*: Anexat (Анексат); *S.Afr.*: Anexate; *Singapore*: Anexate; *Spain*: Anexate; *Swed.*: Lanexat; *Switz.*: Anexate; *Thai.*: Anexate; *Turk.*: Anexate; *UK*: Anexate†; *USA*: Romazicon; *Venez.*: Lanexat.

Pharmacopoeial Preparations
USP 36: Flumazenil Injection.

Fomepizole *(BAN, USAN, rINN)*

Fomepitsoli; Fomepizol; Fomépizole; Fomepizolum; 4-Methylpyrazole; 4-MP; Фомепизол.

4-Methyl-1*H*-pyrazole.
$C_4H_6N_2$=82.11
CAS — 7554-65-6.
ATC — V03AB34.
ATC Vet — QV03AB34.
UNII — 83LCM6L28Y.

Uses and Administration

Fomepizole is a competitive inhibitor of alcohol dehydrogenase. It is used for the treatment of poisoning by ethylene glycol (p. 2500.3) or methyl alcohol (p. 2196.3), which are converted to toxic metabolites by alcohol dehydrogenase. Fomepizole is given in a loading dose of 15 mg/kg followed by 10 mg/kg every 12 hours for 4 doses; the dose should then be increased to 15 mg/kg every 12 hours until serum concentrations of ethylene glycol or methyl alcohol are less than 20 mg per 100 mL. All doses should be given by intravenous infusion over 30 minutes in at least 100 mL of sodium chloride 0.9% or glucose 5%. In patients who also require haemodialysis, doses of fomepizole should be given every 4 hours during haemodialysis sessions. Alternatively, the *National Poisons Information Service* in the UK suggests that a loading dose of 15 mg/kg can be infused over 30 to 45 minutes, followed by a continuous infusion of 1 mg/kg per hour for the duration of the haemodialysis.

Fomepizole has also been given similarly as the sulfate and the hydrochloride.

References.

1. Baum CR, *et al.* Fomepizole treatment of ethylene glycol poisoning in an infant. *Pediatrics* 2000; 106: 1489–91.
2. Brent J, *et al.* Fomepizole for the treatment of methanol poisoning. *N Engl J Med* 2001; 344: 424–9.
3. Battistella M. Fomepizole as an antidote for ethylene glycol poisoning. *Ann Pharmacother* 2002; 36: 1085–9.
4. Mycyk MB, Leikin JB. Antidote review: fomepizole for methanol poisoning. *Am J Ther* 2003; 10: 68–70.
5. Brent J. Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med* 2009; 360: 2216–23.
6. Brent J. Fomepizole for the treatment of pediatric ethylene and diethylene glycol, butoxyethanol, and methanol poisonings. *Clin Toxicol* 2010; 48: 401–6.

Administration. It has been suggested[1] that the evidence for rapid autoinduction of fomepizole metabolism, and the consequent need for an increase in dosage after the first 4 maintenance doses, is capable of more than one interpretation, and that an alternative regimen of 20 mg/kg intravenously every 12 hours throughout treatment might be equally effective and more convenient. However, further study in the relevant patient groups is needed before any change in regimen can be recommended.

1. Bestic M, *et al.* Fomepizole: a critical assessment of current dosing recommendations. *J Clin Pharmacol* 2009; 49: 130–7.

Adverse Effects and Precautions

Fomepizole is generally well tolerated. The most frequent adverse effects associated with fomepizole are headache, nausea, dizziness, drowsiness, and taste disturbances. Other less common adverse effects include abdominal or back pain, fever, rash and other hypersensitivity reactions, gastrointestinal disturbances, hypotension, tachycardia or bradycardia, shock, anuria, multi-organ system failure, disseminated intravascular coagulation, anaemia, lymphangitis, pharyngitis, and hiccups. Nervous system reactions include seizures, lightheadedness, agitation, anxiety, vertigo, flushing, nystagmus, abnormal smell, and speech or visual disturbances.

Injection site reactions have been reported; fomepizole should not be given undiluted or by bolus injection. Transient increases in hepatic enzyme values and eosinophilia have been noted with repeated dosing, and liver function tests and blood counts should be monitored.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fomepizole as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Fomepizole inhibits alcohol dehydrogenase and thus reduces the rate of elimination of alcohol by about 40%; similarly alcohol reduces the rate of elimination of fomepizole by about 50%. Fomepizole also induces cytochrome P450 isoenzymes and could potentially interact with other drugs that affect this enzyme system.

Pharmacokinetics

Fomepizole is absorbed from the gastrointestinal tract but is usually given intravenously. It is metabolised in the liver, mainly to 4-carboxypyrazole; the metabolites are excreted in the urine, with only a small amount of unchanged drug. After multiple doses, fomepizole induces its own metabolism by the cytochrome P450 enzyme system, significantly increasing the rate of elimination. Fomepizole is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Antizol; *Israel*: Antizol; *UK*: Antizol; *USA*: Antizol.

Fuller's Earth

Argile Smectique; Argilla Smectica; Bleicherde; Terra Fullonica; Terre à Foulon; Tierra de Fuller; Фуллерова Земля.
CAS — 8031-18-3.

Profile

Fuller's earth is a clay-like substance (smectite) related to kaolin (p. 1850.1) and bentonite (p. 2170.3) that has the ability to adsorb impurities or colouring from fats, grease, or oils. It consists mainly of hydrated aluminium silicates that contain exchangeable metal cations such as magnesium, sodium, and calcium within their structure. Clay minerals that occur in varying amounts in Fuller's earth include montmorillonite, kaolinite, attapulgite or palygorskite, and halloysite. Fuller's earth has been used in the management of paraquat poisoning (p. 2159.2), although activated charcoal is now generally preferred. It has also been used for its adsorbent properties in various dermatological preparations, as a cat litter, as a stain remover, and in industry as a refining, filtering, or decolorising medium.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Camomila.

Fytic Acid *(rINN)*

Acide Fytique; Ácido fítico; Acidum Fyticum; Inositol Hexaphosphate; Inositolhexaphosphoric Acid; Phytic Acid; Фэтовая Кислота.

1,2,3,4,5,6-Cyclohexanehexolphosphoric acid; *Myo*-inositol-hexakis(dihydrogen phosphate).
$C_6H_{18}O_{24}P_6$=660.0
CAS — 83-86-3.
UNII — 7IGF0S7R8I.

Calcium Magnesium Fytate *(rINNM)*

Calcii Magnesii Fytas; Calcium Magnesium Inositol Hexaphosphate; Calcium Magnesium Phytate; Fitato de calcio y magnesio; Fitina; Fytate de Calcium Magnésium; Inositocalcium; Phytin; Кальция Магния Фэитат.
CAS — 3615-82-5.
UNII — N1DEP08LNK.

Pharmacopoeias. In *Viet.*

Sodium Fytate *(rINNM)*

Fitato de sodio; Fitato sódico; Fytate de Sodium; Natrii Fytas; Phytate Sodium (USAN); Sodium cyclohexanehexyl(hexaphosphate); Sodium Phytate; SQ-9343; Натрий Фэитат.
$C_6H_9Na_2O_{24}P_6$=857.9
CAS — 7205-52-9.
UNII — 88496G1ERL.

Profile

Fytic acid is a phosphorus compound with chelating actions. It occurs naturally in plants as the insoluble calcium magnesium salt and is a major source of phosphate in the diet, although there is debate about its bioavailability. Excess intake of fytate has been associated with deficiencies of elements such as calcium, iron, and zinc.

Fytic acid has been used in topical preparations for the treatment of skin hyperpigmentation, where it is claimed to reduce the action of enzymes involved in melanogenesis. Calcium magnesium fytate has been used as a tonic. Sodium fytate reacts with calcium in the gastrointestinal tract to form non-absorbable calcium fytate which is excreted in the faeces. Sodium fytate has been used in a similar manner to sodium cellulose phosphate (p. 1574.2) to reduce the absorption of calcium from the gut in the treatment of hypercalciuria. It also binds other metals.

Sodium fytate labelled with technetium-99m (p. 2228.1) has been used intravenously for imaging of the liver.

References.

1. Zhou JR, Erdman JW. Phytic acid in health and disease. *Crit Rev Food Sci Nutr* 1995; 35: 495–508.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Phytat DB†; *Hung.*: Fyton; *Singapore*: Nu-Derm Exfoderm.

Multi-ingredient Preparations. *Braz.*: Libiplus; *Fr.*: Vitathion; *Ital.*: Lightening; Phytic Acid; *Port.*: Cebrotex Forte†; Relavit Fosforo; *Spain*: Fosgluten Reforzado†; *Turk.*: Calcidine; *Ukr.*: Quadevit (Квадевит).

Glucagon *(BAN, rINN)*

Glikagonas; Glucagó; Glucagón; Glucagone; Glucagonum; Glukagon; Glukagoni; HGF; Глюкагон.

His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr.

$C_{153}H_{225}N_{43}O_{49}S$=3482.8

CAS — 16941-32-5.

ATC — H04AA01.

ATC Vet — QH04AA01.

UNII — 76LA80IG2G.

Pharmacopoeias. In *US*.

USP 36: (Glucagon). A polypeptide hormone obtained from porcine and bovine pancreas glands. A fine, white or faintly coloured, practically odourless, crystalline powder. Soluble in dilute alkali and acid solutions; insoluble in most organic solvents. Store under nitrogen in airtight glass containers at a temperature of 2 degrees to 8 degrees.

Uses and Administration

Glucagon is an endogenous polypeptide hormone that is produced by the alpha cells of the pancreatic islets of Langerhans. It is a hyperglycaemic that mobilises glucose by activating hepatic glycogenolysis. Glucagon for therapeutic use may be derived from animal sources but is now more commonly produced using recombinant DNA techniques. It is usually given as the hydrochloride, but doses are expressed as glucagon (note that 1 unit is equivalent to 1 mg of glucagon).

Glucagon is used in the treatment of severe hypoglycaemic reactions when the patient cannot take glucose orally and intravenous glucose is not feasible. It is given by subcutaneous, intramuscular, or intravenous injection in a dose of 1 mg. If there is no response within 10 minutes, intravenous glucose should be given, although there is no contra-indication to repeating the dose of glucagon. Once the patient has responded sufficiently to take carbohydrate orally this should be given to restore liver glycogen stores and prevent relapse of hypoglycaemia.

As glucagon reduces the motility of the gastrointestinal tract it is used as a diagnostic aid in gastrointestinal examinations. The route of administration and dose is dependent upon the diagnostic procedure. A dose of 1 to 2 mg intramuscularly has an onset of action of 4 to 15 minutes and a duration of effect of 10 to 40 minutes; 0.2 to 2 mg intravenously produces an effect within 1 minute that lasts for 5 to 25 minutes. A usual dose for relaxation of the stomach, duodenum, and small bowel is 200 to 500 micrograms intravenously or 1 mg intramuscularly. To relax the colon 500 to 750 micrograms is given intravenously or 1 to 2 mg intramuscularly.

For doses in children, see below.

Glucagon possesses positive cardiac inotropic activity but is not generally considered suitable for heart failure. However, it is used in the treatment of beta-blocker overdosage, see Cardiovascular Effects, below.

Action. References.

1. Habegger KM, *et al.* The metabolic actions of glucagon revisited. *Nat Rev Endocrinol* 2010; 6: 689–97.
2. Taborsky GJ. The physiology of glucagon. *J Diabetes Sci Technol* 2010; 4: 1338–44.

Administration. Glucagon is licensed for use by subcutaneous, intramuscular, and intravenous injection for hypoglycaemia, but intranasal[1] and rectal[2] formulations have also been investigated.

1. Teshima D, *et al.* Nasal glucagon delivery using microcrystalline cellulose in healthy volunteers. *Int J Pharm* 2002; 233: 61–6.
2. Parker DR, *et al.* Glucagon is absorbed from the rectum but does not hasten recovery from hypoglycaemia in patients with type 1 diabetes. *Br J Clin Pharmacol* 2008; 66: 43–9.

Administration in children. Glucagon is used in children for the treatment of severe hypoglycaemia associated with diabetes. It can be given by subcutaneous, intramuscular, or intravenous injection, usually as the hydrochloride, although doses are expressed as glucagon. A dose of 500 micrograms is recommended for children weighing less than 25 kg or younger than 6 to 8 years of age. Older patients or those weighing more than 25 kg should be given the adult dose, see above. The *BNFC* suggests a dose of 20 micrograms/kg in neonates. Intravenous glucose is required if there is no response within 10 minutes, and oral carbohydrates should be given once the patient has responded to prevent relapse.

Glucagon is used as a diagnostic aid in gastrointestinal examinations as it reduces the motility of the gastrointestinal tract. The dose depends on the procedure, see Uses and Administration, above.

The *BNFC* also suggests glucagon doses for treatment of endogenous hyperinsulinaemia in young children, although unlicensed for this indication in the UK. Neonates may be given a single dose of 200 micrograms/kg (to a maximum of 1 mg), and children from 1 month to 2 years of age a dose of 1 mg, by intravenous or intramuscular injection. Alternatively, doses may be given by continuous intravenous infusion:

- neonate: 1 to 18 micrograms/kg per hour adjusted according to response, to a maximum of 50 micrograms/kg per hour
- 1 month to 2 years: 1 to 10 micrograms/kg per hour, increased if necessary

For further discussion of glucagon use for hypoglycaemia, see below. Glucagon can also be used in children for management of beta-blocker overdose, see Cardiovascular Effects, below, or to measure growth hormone secretion, see Diagnosis and Testing, below.

Cardiovascular effects. Glucagon has chronotropic and inotropic effects due to its ability to raise cyclic AMP concentrations independently of a response to catecholamines.[1] It is used in the management of beta-blocker overdosage (p. 1320.2), although evidence of benefit is mainly anecdotal;[2] doses of 2 to 10 mg (or 50 to 150 micrograms/kg in children, to a maximum of 10 mg) by intravenous injection, followed by an infusion of 50 micrograms/kg per hour, have been suggested.

Glucagon may also have a role in anaphylactic shock (see under Adrenaline, p. 1293.2), particularly in patients receiving beta blockers, in whom adrenaline may be less effective. A dramatic improvement in refractory hypotension during an anaphylactic reaction to contrast media was described in a 75-year-old man receiving beta blockers after intravenous glucagon.[3]

There has also been a report[4] of benefit with intravenous glucagon after calcium-channel blocker overdosage, but evidence from controlled studies is not available[2] and glucagon is not generally regarded as standard treatment for such patients.

1. White CM. A review of potential cardiovascular uses of intravenous glucagon administration. *J Clin Pharmacol* 1999; 39: 442–7.
2. Bailey B. Glucagon in β-blocker and calcium channel blocker overdoses: a systematic review. *J Toxicol Clin Toxicol* 2003; 41: 595–602.
3. Zaloga GP, *et al.* Glucagon reversal of hypotension in a case of anaphylactic shock. *Ann Intern Med* 1986; 105: 65–6.
4. Walter FG, *et al.* Amelioration of nifedipine poisoning associated with glucagon therapy. *Ann Emerg Med* 1993; 22: 1234–7.

Diagnosis and testing. Glucagon stimulates secretion of growth hormone and cortisol (hydrocortisone) and has been used as a test of pituitary function in adults,[1-3] and in children.[4-7] It may be particularly suitable when first-line tests such as the insulin-tolerance test are contra-indicated.[3,8] Although unlicensed in the UK for this indication, the *BNFC* suggests glucagon 100 micrograms/kg (to a maximum of 1 mg) as a single intramuscular dose in children from 1 month to 18 years of age. It has also been given by subcutaneous injection in a dose of 50 micrograms/kg.[9] The glucagon stimulation test should be used with caution in young children;[5] severe secondary hypoglycaemia and death has been reported[10] in a 2-year-old child after a glucagon test for growth hormone secretion.

1. Gómez JM, *et al.* Growth hormone release after glucagon as a reliable test of growth hormone assessment in adults. *Clin Endocrinol (Oxf)* 2002; 56: 329–34.
2. Abs R. Update on the diagnosis of GH deficiency in adults. *Eur J Endocrinol* 2003; 148: S3–S8.
3. Ho KKY. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, Japan Endocrine Society, and Endocrine Society of Australia. *Eur J Endocrinol* 2007; 157: 695–700. Also available at: http://www.ghresearchsociety.org/files/2007_Consensus_AGHD.pdf (accessed 18/07/08)
4. Hindmarsh PC, Swift PGF. An assessment of growth hormone provocation tests. *Arch Dis Child* 1995; 72: 362–8.
5. GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. *J Clin Endocrinol Metab* 2000; 85: 3990–3. Also available at: http://www.ghresearchsociety.org/files/Eilat.pdf (accessed 04/10/05)
6. di Iorgi N, *et al.* The accuracy of the glucagon test compared to the insulin tolerance test in the diagnosis of adrenal insufficiency in young children with growth hormone deficiency. *J Clin Endocrinol Metab* 2010; 95: 2132–9.
7. Secco A, *et al.* The glucagon test in the diagnosis of growth hormone deficiency in children with short stature younger than 6 years. *J Clin Endocrinol Metab* 2009; 94: 4251–7.
8. Cook DM, *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for growth hormone use in growth hormone-deficient adults and transition patients—2009 update: executive summary of recommendations. *Endocr Pract* 2009; 15: 580–6.
9. Kappy MS, *et al.* Assessing adrenal function in primary care settings with a single sample subcutaneous glucagon test. *J Pediatr* 2006; 149: 682–6.
10. Shah A, *et al.* Hazards of pharmacologic tests of growth hormone secretion in childhood. *BMJ* 1992; 304: 173–4.

Gastrointestinal disorders. The relaxant effect of glucagon on smooth muscle has been used to facilitate passage of swallowed foreign bodies[1] and impacted food boluses[2] that have become lodged in the lower oesophagus. However, a controlled study[3] in children with impacted oesophageal coins found that glucagon was not effective and it has been suggested that it should not be used as first-line therapy.[4]

1. Cooke MW, Glucksman EE. Swallowed coins. *BMJ* 1991; 302: 1607.
2. Parrugia M, *et al.* Radiological treatment of acute oesophageal food impaction. *Br J Hosp Med* 1995; 54: 410–11.
3. Mehta D, *et al.* Glucagon use for esophageal coin dislodgment in children: a prospective, double-blind, placebo-controlled trial. *Acad Emerg Med* 2001; 8: 200–3.
4. Arora S, Gallich P. Myth: glucagon is an effective first-line therapy for esophageal foreign body impaction. *CJEM* 2009; 11: 169–71.

Hypoglycaemia. Hypoglycaemia most commonly occurs in diabetic patients, particularly those receiving insulin therapy. Other rare causes include alcohol ingestion and tumours such as insulinomas. Neonatal hypoglycaemia occurs in small-for-gestational-age infants or infants of diabetic mothers. Persistent or recurrent hypoglycaemia in neonates is usually due to an endocrine or metabolic disorder, such as nesidioblastosis.

Glucose is the treatment of choice for acute hypoglycaemia since it corrects the problem at source. In patients who are unconscious or unable to take glucose orally, it may need to be given intravenously. Glucagon is an alternative in such situations, and first-line use has been suggested[1] since it is more convenient and easier to give than parenteral glucose, particularly in emergency situations. However, glucagon has a slower onset and may not always be effective, particularly where hepatic glycogen stores are depleted, such as in patients with alcohol-induced hypoglycaemia or with insulinoma. Low doses of glucagon have also been given prophylactically[2] in diabetic children at risk of developing hypoglycaemia due to gastrointestinal disorders or reduced oral intake.

Hypoglycaemia in neonates is usually managed by adjusting the enteral feeds or by giving parenteral glucose in symptomatic infants. Glucagon may be used if parenteral glucose is not effective or cannot be given.[3,4] In infants with persistent hyperinsulinaemic hypoglycaemia, continuous infusion of glucagon has been used, although oral treatments such as diazoxide plus chlorothiazide are usually preferred. Nifedipine has been added in resistant cases.[5] Pancreatectomy is often required in infants who are not responsive to diazoxide, although subcutaneous octreotide and frequent feeds have been used to manage symptoms in some infants with diffuse disease.[6]

Intractable hypoglycaemia (such as that resulting from excessive endogenous insulin production from islet cell tumours or hyperplasia) is usually treated with diazoxide, but continuous infusion of glucagon has been used in patients with tumour-associated hypoglycaemia.[7,8]

1. Gibbins RL. Treating hypoglycaemia in general practice. *BMJ* 1993; 306: 600–1.
2. Haymond MW, Schreiner B. Mini-dose glucagon rescue for hypoglycemia in children with type 1 diabetes. *Diabetes Care* 2001; 24: 643–5.
3. Carter PE, *et al.* Glucagon for hypoglycaemia in infants small for gestational age. *Arch Dis Child* 1988; 63: 1264.
4. Williams AF. Hypoglycaemia of the newborn: a review. *Bull WHO* 1997; 75: 261–90.
5. Aynsley-Green A, *et al.* Practical management of hyperinsulinism in infancy. *Arch Dis Child Fetal Neonatal Ed* 2000; 82: F98–F107.
6. Kapoor RR, *et al.* Hyperinsulinaemic hypoglycaemia. *Arch Dis Child* 2009; 94: 450–7.
7. Samaan NA, *et al.* Successful treatment of hypoglycemia using glucagon in a patient with an extrapancreatic tumor. *Ann Intern Med* 1990; 113: 404–6.
8. Hoff AO, Vassilopoulou-Sellin R. The role of glucagon administration in the diagnosis and treatment of patients with tumor hypoglycemia. *Cancer* 1998; 82: 1585–92.

Adverse Effects

Nausea and vomiting may occur after use of glucagon. Hypersensitivity reactions (including rash and anaphylactic shock), abdominal pain, hypotension or hypertension, tachycardia or bradycardia, and hypokalaemia have also been reported.

Precautions

Glucagon should generally not be given to patients with phaeochromocytoma since it can cause a release of catecholamines producing marked hypertension. Glucagon should be given with care to patients with insulinoma as the increase in blood glucose may stimulate insulin secretion. Glucagon was formerly used to diagnose phaeochromocytoma and insulinoma but this use has been largely abandoned. Caution is also required when it is being used as a diagnostic aid in glucagonoma, or in diabetic patients or elderly patients with heart disease.

Glucagon is not effective in patients with marked depletion of liver glycogen stores, as in starvation, adrenal insufficiency, alcohol-induced hypoglycaemia, or chronic hypoglycaemia. Oral carbohydrates should be given after glucagon to prevent relapse of hypoglycaemia.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies glucagon as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pregnancy. Although data are scarce, there are reports of the use of glucagon during pregnancy for hypoglycaemia or as an inotrope, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Interactions

The hyperglycaemic effect of glucagon is antagonised by insulin, and caution is needed when using glucagon as a diagnostic agent in diabetic patients. Beta blockers and indometacin may also reduce glucagon's hyperglycaemic effect. Glucagon inhibits gastrointestinal motility and an additive effect may be seen with antimuscarinic drugs.

Warfarin. For a report of glucagon enhancing the anticoagulant effect of warfarin, see p. 1534.2.

Pharmacokinetics

Glucagon has a plasma half-life of about 3 to 6 minutes but longer values have been reported in diabetics (see Bioavailability, below). It is inactivated in the liver, kidneys, and plasma.

Bioavailability. In a study[1] in healthy subjects and diabetic patients the bioavailability of glucagon given intranasally was about 30% of that after intramuscular injection. However, the mean value for the apparent half-life after intramuscular injection was 28.6 and 31.4 minutes respectively in the two groups, compared with 6.6 and 11.9 minutes for intravenous infusion, and 5.5 and 13.8 minutes when given intranasally, possibly due to slow release of glucagon from the injection site.

1. Pontiroli AE, *et al.* Pharmacokinetics of intranasal, intramuscular and intravenous glucagon in healthy subjects and diabetic patients. *Eur J Clin Pharmacol* 1993; 45: 535–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: GlucaGen; *Austral.*: GlucaGen; *Austria*: GlucaGen; *Belg.*: GlucaGen; *Braz.*: GlucaGen; *Canad.*: GlucaGen; *Chile*: GlucaGen; *China*: GlucaGen; *Cz.*: GlucaGen; *Denm.*: GlucaGen; *Fin.*: GlucaGen; *Fr.*: GlucaGen; *Ger.*: GlucaGen; *Gr.*: GlucaGen; *Hong Kong*: GlucaGen; *Hung.*: GlucaGen; *India*: GlucaGen; Glugon; *Irl.*: GlucaGen; *Israel*: GlucaGen; *Ital.*: GlucaGen; *Malaysia*: GlucaGen; *Neth.*: GlucaGen; *NZ*: GlucaGen; *Pol.*: GlucaGen; *Port.*: GlucaGen; *Rus.*: GlucaGen (Глюкаген); *S.Afr.*: GlucaGen; *Singapore*: GlucaGen; *Spain*: GlucaGen; *Switz.*: GlucaGen; *Turk.*: GlucaGen; *UK*: GlucaGen; *Ukr.*: GlucaGen (ГлюкаГен); *USA*: GlucaGen.

Pharmacopoeial Preparations
BP 2014: Human Glucagon for Injection;
USP 36: Glucagon for Injection.

Glucarpidase *(dINN)*

Carboxypeptidase G_2; Glucarpidasa; Glucarpidasum; Глюкарпидаз.
CAS — 9074-87-7.
ATC — V03AF09.
ATC Vet — QV03AF09.
UNII — 2GFP98JD79.

Uses and Administration

Glucarpidase is a recombinant glutamate carboxypeptidase that hydrolyses methotrexate to inactive metabolites; it is used in the management of methotrexate toxicity (plasma concentrations of > 1 micromol/litre) in patients with delayed methotrexate clearance due to impaired renal function (p. 826.3). A single intravenous bolus injection of glucarpidase 50 units/kg is given over 5 minutes.

Treatment with folinic acid rescue should be continued when glucarpidase is given (but see Interactions, below). For the first 48 hours after glucarpidase, the dose of folinic acid should be based on the patient's methotrexate concentration before glucarpidase was given; thereafter, the dose is based on measured methotrexate concentrations. *Methotrexate concentrations within 48 hours of a dose of glucarpidase can only be reliably measured by a chromatographic method. Measurement of methotrexate using immunoassays during this time period is unreliable as an inactive metabolite of methotrexate (with a half-life of about 9 hours) interferes with the measurement resulting in an overestimation of the methotrexate concentration.* For further information on folinic acid rescue, see under Sodium Folinate, p. 2067.1.

References.

1. Widemann BC, *et al.* Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. *J Natl Cancer Inst* 2004; 96: 1557–9.
2. Buchen S, *et al.* Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 2005; 92: 480–7.
3. Schwartz S, *et al.* Glucarpidase (carboxypeptidase g2) intervention in adult and elderly cancer patients with renal dysfunction and delayed methotrexate elimination after high-dose methotrexate therapy. *Oncologist* 2007; 12: 1299–1308.
4. Phillips M, *et al.* Pharmacokinetics of glucarpidase in subjects with normal and impaired renal function. *J Clin Pharmacol* 2008; 48: 279–84.
5. Patterson DM, Lee SM. Glucarpidase following high-dose methotrexate: update on development. *Expert Opin Biol Ther* 2010; 10: 105–11.
6. Widemann BC, *et al.* Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol* 2010; 28: 3979–86.

Adverse Effects and Precautions

The most common adverse effects associated with the use of glucarpidase may include paraesthesias, flushing, nausea and/or vomiting, hypotension, and headache. Less commonly it may also cause serious allergic reactions including anaphylaxis.

Interactions

Treatment with folinic acid rescue should be continued when glucarpidase is given. However, because folinic acid is a substrate for glucarpidase, it should not be given within 2 hours before or after a dose of glucarpidase. Similarly, glucarpidase may also interact with reduced folates and folate inhibitors.

Pharmacokinetics

The mean elimination half-life of glucarpidase, in the absence of methotrexate, is 5.6 hours; in severe renal impairment (creatinine clearance less than 30 mL/min) this rises to 8.2 hours. The mean volume of distribution is 3.6 litres indicating that glucarpidase is mostly found in the plasma.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Voraxaze.

Glutathione *(BAN)*

Glutathion; Glutathionum; Glutation; Glutation; Glutationas; Glutationi; GSH; Глутатион.
N-(*N*-L-γ-Glutamyl-L-cysteinyl)glycine
$C_{10}H_{17}N_3O_6S$=307.3
CAS — 70-18-8.
ATC — V03AB32.
ATC Vet — QV03AB32.
UNII — GAN16C9B8O.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn.* and *US.*

Ph. Eur. 8: (Glutathione). Fermentation product. A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Glutathione). Store in airtight containers.

Profile

Glutathione is an endogenous peptide with antioxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin and other platinum derivatives; they have also been tried to prevent other adverse effects of antineoplastic and radiation therapy, as well as being promoted for a very broad range of disorders including heavy metal poisoning, skin pigmentation disorders, liver disorders, dyspepsia, hypersensitivity reactions, and pre-eclampsia. It has been added to nutritional supplements and eye irrigation solutions, sometimes as the disulfide, oxiglutatione. Glutathione has also been investigated for lung disorders (see below). A liposomal formulation of glutathione has been tried as a replacement therapy in patients with inborn errors of glutathione metabolism.

Antineoplastic toxicity. Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomised study[1] in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity. Benefit has also been seen in small randomised studies in patients receiving oxaliplatin.[2,3]

1. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995; 13: 26–32.
2. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2002; 20: 3478–83.
3. Milla P, *et al.* Administration of reduced glutathione in FOLFOX4 adjuvant treatment for colorectal cancer: effect on oxaliplatin pharmacokinetics, Pt-DNA adduct formation, and neurotoxicity. *Anticancer Drugs* 2009; 20: 396–402.

Lung disorders. Glutathione is an important extracellular antioxidant in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulised glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with idiopathic pulmonary fibrosis[1] and in cystic fibrosis,[2] but the clinical effects of these changes are not clear. Another study in cystic fibrosis[3] found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function, an effect also noted in another small study.[4]

Benefit has also been reported[5] with glutathione in a patient with emphysema. However, in a study[6] of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.

1. Borok Z, *et al.* Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet* 1991; 338: 215–16.
2. Roum JH, *et al.* Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. *J Appl Physiol* 1999; 87: 438–43.
3. Griese M, *et al.* Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. *Am J Respir Crit Care Med* 2004; 169: 822–8.
4. Bishop C, *et al.* A pilot study of the effect of inhaled buffered reduced glutathione on the clinical status of patients with cystic fibrosis. *Chest* 2005; 127: 308–17.
5. Lamson DW, Brignall MS. The use of nebulized glutathione in the treatment of emphysema: a case report. *Altern Med Rev* 2000; 5: 429–31.
6. Marrades RM, *et al.* Nebulized glutathione induces bronchoconstriction in patients with mild asthma. *Am J Respir Crit Care Med* 1997; 156: 425–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: A Tuo Mo Lan (阿拓莫兰); Gan Zhi (甘志); Ge La Da Xin (格拉达欣); Lv Ting Nuo (绿汀诺); Neuthione (乃奇安); Song Tai Si (松泰斯); Tad (泰特); Tian Yi (天亿); *Hong Kong*: Glu-tathion; TAD; *India*: Glutasoz; Gluton; *Ital.*: Gluthion; Ridutox; Rition; TAD; Tationil; *Jpn*: Glutathin†; Tathion; *Philipp.*: Gluta; *Rus.*: Glutoxim (Глутоксим); *USA*: Cachexon.

Multi-ingredient Preparations. *Austral.*: BSS Plus†; *Canad.*: BSS Plus; Vitathion-ATP†; *Fr.*: BSS Compose†; *Ger.*: BSS Plus; *Hung.*: BSS Plus†; *India*: Basol Plus; DSN; I-Site; Imunolife; Macuchek; Oxyeye; *Indon.*: nutrivision; *Israel*: BSS Plus; *Ital.*: Biotad; Endoepatox; Preastig; Puraflor; Riduton Ergo; *Malaysia*: BSS Plus; *Mex.*: Avitil; *Philipp.*: Illumina; Nutrof†; *S.Afr.*: BSS Plus; Vita-Thion; *Singapore*: BSS Plus; Essentials†; Nutrivision†; *Spain*: Tomevit†; *Thai.*: BSS Plus; *Turk.*: BSS Plus; *UK*: Neurozan; *USA*: BSS Plus; PowerMate; Sucrets Defense Kids Formula.

Haem Derivatives

Heme Derivatives; Hemo, derivados del grupo; Производные Гема.
ATC — B06AB01 (Haematin).
ATC Vet — QB06AB01 (haematin).

Profile

Haem is the iron protoporphyrin constituent of haemoglobin and is responsible for its colour and oxygen-carrying capacity. It is used in the management of porphyrias (p. 1556.1). Haem is given intravenously as its derivatives, although there is some confusion over their terminology. The names haematin (hematin) and haemin (hemin) have been used interchangeably although chemically haematin is the hydroxy derivative, formed by the reaction of haemin and sodium carbonate in solution. The arginine salt (haem arginate; haemin arginate; heme arginate) is reported to be more stable.

Haem arginate is used in the treatment of acute hepatic porphyrias, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria. It is given by slow intravenous infusion in a dose of 3 mg/kg daily for 4 days, infused over at least 30 minutes. The maximum recommended dose is 250 mg daily. The course may be repeated, with close monitoring, in patients with an inadequate response.

Haematin (haemin formulated for injection with sodium carbonate) is used intravenously for recurrent attacks of acute intermittent porphyria associated with the menstrual cycle in patients unresponsive to other therapy. It is given in a usual dose of 1 to 4 mg/kg daily for 3 to 14 days as an intravenous infusion over 10 to 15 minutes. In severe cases the dose may be repeated after 12 hours, but no more than 6 mg/kg should be given in any 24 hour period.

Injection site reactions may occur after infusion of haem derivatives and they should be given into a large arm vein or central vein which is then flushed with sodium chloride 0.9%. Use of a filter is recommended due to the colour of

the infusion. Increased serum ferritin concentrations have been reported after prolonged use of haem derivatives, and transient mild anticoagulant effects have been noted with haematin.

Administration. Lyophilised formulations of haematin, formulated as haemin with sodium carbonate, are usually reconstituted with water. However, in order to maximise stability and prevent the formation of degradation products that can cause adverse effects it has been suggested that it may be given as haem albumin by reconstituting with an equimolar amount of albumin 25% instead.[1]

1. Anderson KE, *et al.* Reconstitution of hematin for intravenous infusion. *Ann Intern Med* 2006; 144: 537–8.

Administration in children. Attacks of porphyria are uncommon in children, but UK licensed product information for haem arginate notes that limited experience in tyrosinaemia suggests that a dose of not more than 3 mg/kg daily may safely be given for 4 days.

Porphyrias. The porphyrias are a group of inherited and acquired disorders of haem biosynthesis in which defects in specific enzymes lead to the accumulation of haem precursors, including aminolevulinic acid, porphobilinogen, and porphyrins.[1-12] They are generally classified as acute or non-acute, reflecting their clinical presentation, or as hepatic or erythropoietic, depending on the site of the enzyme defect. The three most common forms are acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria.

ACUTE PORPHYRIAS. These are inherited disorders characterised by the accumulation of porphyrin precursors, leading to acute attacks of neurovisceral symptoms. The most common form is ***acute intermittent porphyria*** (acute hepatic porphyria); ***variegate porphyria*** and ***hereditary coproporphyria*** are generally less common forms in which there is accumulation of both porphyrin precursors and porphyrins, leading to acute attacks with cutaneous symptoms similar to those seen in non-acute porphyrias (see below).

In acute porphyrias, some enzyme activity is present and the defect only becomes apparent when demand for hepatic haem is increased. Attacks are rare before puberty and the disorder may remain latent in many patients. The presenting symptom is most commonly severe abdominal pain; other gastrointestinal symptoms such as nausea and vomiting also occur, along with autonomic effects including hypertension, tachycardia, sweating, pallor, and pyrexia. Convulsions may occur at the peak of an attack and may persist between attacks. Neuropathy leads to weakness and paralysis and may progress rapidly to respiratory distress. Psychiatric symptoms are also common, particularly agitation, anxiety, and behavioural disturbances. Various factors can increase the demand for haem and attacks are usually precipitated by drugs, alcohol, smoking, steroid hormones, reduced caloric intake, or infection. They typically last for several days and are followed by complete recovery, although in some patients chronic abdominal pain may persist without other symptoms.

The primary management of an attack is to remove precipitants and to provide intensive support. **Symptomatic treatment** is complicated by the wide range of drugs that may precipitate porphyria. High doses of parenteral opioids may be required for pain; there is a danger of addiction occurring, but this is rare unless attacks are frequent or pain persists between attacks. Phenothiazines such as chlorpromazine are useful to control nausea and agitation and their sedative effect may also be beneficial. High doses of propranolol may be required for cardiovascular symptoms. Assisted ventilation may be necessary. Convulsions usually disappear as the attack resolves; management of patients who have convulsions between attacks is a therapeutic problem since many antiepileptics are porphyrinogenic (see Porphyria, p. 512.1). **Specific therapy** is aimed at suppressing the haem biosynthetic pathway, to prevent further accumulation of precursors. Haem, given as either haematin or haem arginate, is the most effective treatment and should be given as soon as possible after onset of the attack; it produces feedback suppression of the biosynthetic pathway. Tin-protoporphyrin, a haem oxygenase inhibitor, has been given with haem to prolong its action but is not commercially available. A high carbohydrate intake may also suppress haem precursor production and should be ensured in all patients, especially if haem is not immediately available; it is usually given orally to prevent fluid overload and exacerbation of hyponatraemia, but intravenous glucose may be required in patients who are vomiting. **Prevention** of attacks involves avoiding drugs that precipitate porphyria and maintaining an adequate carbohydrate intake. Gonadorelin analogues, such as buserelin, may have a role in preventing attacks related to the menstrual cycle. Long-term treatment with haem has been tried in patients with frequent attacks.

NON-ACUTE PORPHYRIAS. These are characterised by the accumulation of porphyrins and usually present with cutaneous symptoms, although porphyrins also accumulate in the liver and liver damage commonly occurs. ***Porphyria cutanea tarda*** (cutaneous hepatic porphyria) is the most common form of porphyria. It is usually an acquired disorder and there is an association with moderate or heavy alcohol intake and hepatitis C. There is usually a raised serum-iron concentration and use of oestrogen has also been implicated. The main clinical symptom is cutaneous photosensitivity leading to bullous dermatosis, pruritus, and skin fragility, in areas exposed to sunlight. **Management** involves protecting the skin from sunlight and trauma and avoiding causative agents such as alcohol and iron. Sunscreen preparations must be based on zinc oxide or titanium dioxide to be effective. Reduction of serum-iron concentrations by phlebotomy restores enzyme function and is effective in most patients; it should be carried out every 1 to 2 weeks until remission occurs, and may be required periodically for maintenance. Chloroquine and hydroxychloroquine have also been used and may be effective where phlebotomy is contra-indicated; they appear to act by complexing with porphyrins and increasing their excretion, but low doses are necessary to avoid exacerbating the condition. An alternative method of reducing serum-iron is with the iron chelator desferrioxamine, although it may be less effective than phlebotomy; it is usually reserved for patients unable to tolerate phlebotomy. In patients with renal failure who are too anaemic for phlebotomy and who cannot excrete chloroquine, erythropoietin may be used, and may be combined with desferrioxamine or low-volume phlebotomy.

Erythropoietic protoporphyria is a less common non-acute porphyria and is an inherited disorder leading to accumulation of protoporphyrin. Symptoms are cutaneous and there is an acute reaction to sunlight leading to urticaria, pruritus, swelling, redness, and a severe burning sensation; liver damage may also occur. **Management** involves protection of the skin, as for porphyria cutanea tarda. Betacarotene is widely used to increase tolerance to sunlight, although its efficacy is not established; canthaxanthin, another carotenoid, has also been used. Haem administration, as haematin or haem arginate, may be beneficial in suppressing protoporphyrin production. Colestyramine and activated charcoal reduce protoporphyrin levels by interrupting enterohepatic recycling; they also bind other porphyrins and may have a role in rare forms of porphyria such as ***congenital erythropoietic porphyria.***

1. Thadani H, *et al.* Diagnosis and management of porphyria. *BMJ* 2000; 320: 1647–51.
2. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; 26: 225–32.
3. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002; 56: 272–8.
4. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003; 16: 57–64.
5. Lecha M, *et al.* Diagnosis and treatment of the hepatic porphyrias. *Dermatol Ther* 2003; 16: 65–72.
6. Anderson KE, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; 142: 439–50. Correction. *ibid.*; 143: 316.
7. Sassa S. Modern diagnosis and management of the porphyrias. *Br J Haematol* 2006; 135: 281–92.
8. Puy H, *et al.* Porphyrias. *Lancet* 2010; 375: 924–37.
9. American Porphyria Foundation. Information available at: http://www.porphyriafoundation.com (accessed 27/05/11)
10. European Porphyria Initiative. Information available at: http://www.porphyria-europe.org (accessed 27/05/11)
11. Porphyria South Africa. Information available at: http://web.uct.ac.za/depts/porphyria/index.htm (accessed 27/05/11)
12. Norwegian Porphyria Centre (NAPOS). Information available at: http://www.drugs-porphyria.org (accessed 27/05/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Panhematin; ***Austria***: Normosang; ***Belg.***: Normosang; ***Canad.***: Proferrin; ***Denm.***: Normosang; ***Fin.***: Normosang; ***Fr.***: Normosang; ***Ger.***: Normosang; ***Gr.***: Normosang; ***Irl.***: Normosang; ***Ital.***: Normosang; ***Jpn***: Normosang; ***Neth.***: Normosang; ***Port.***: Normosang; ***Spain***: Normosang; ***Swed.***: Normosang; ***Switz.***: Normosang; ***UK***: Normosang; ***USA***: Duofer; Panhematin.

Multi-ingredient Preparations. ***Cz.***: Normosang; ***India***: Hembit.

Lanthanum Carbonate *(USAN)*

Carbonato de lantano; Lanthaan(III)carbonaat; Lanthancarbonat; Lanthaniumcarbonaat; Карбонат Лантана; Углекислый Лантан.

Lanthanum carbonate (2:3) hydrate.

$La_2(CO_3)_3.xH_2O$=457.8 (anhydrous lanthanum carbonate)

CAS — 54451-24-0.

ATC — V03AE03.

ATC Vet — QV03AE03.

UNII — 490D9F069T.

NOTE. The names Lambda and Phosbloc have been used as trade marks for lanthanum carbonate.

Uses and Administration

Lanthanum carbonate is a phosphate binder used for hyperphosphataemia (p. 1776.3) in patients with chronic renal failure. It is given orally as the hydrate, but doses are expressed in terms of elemental lanthanum. The usual initial daily dose is 0.75 to 2.25 g of elemental lanthanum, given in divided doses with meals. The dose should be adjusted every 2 to 3 weeks until an acceptable serum-phosphate concentration is achieved; the usual maintenance dose is 1.5 to 3 g daily in divided doses, but up to 3.75 g daily has been given. The tablets should be chewed thoroughly before swallowing.

Reviews.

1. Joy MS, *et al.* Lanthanum carbonate. *Ann Pharmacother* 2006; 40: 234–40.
2. de Freitas D, *et al.* Lanthanum carbonate—a first line phosphate binder? *Semin Dial* 2007; 20: 325–8.
3. Drüeke TB. Lanthanum carbonate as a first-line phosphate binder: the "cons". *Semin Dial* 2007; 20: 329–32.
4. Sprague SM. A comparative review of the efficacy and safety of established phosphate binders: calcium, sevelamer, and lanthanum carbonate. *Curr Med Res Opin* 2007; 23: 3167–75. Correction. *ibid.* 2008; 24: 708.
5. Barton Pai A, *et al.* Therapeutic use of the phosphate binder lanthanum carbonate. *Expert Opin Drug Metab Toxicol* 2009; 5: 71–81.
6. Curran MP, Robinson DM. Lanthanum carbonate: a review of its use in lowering serum phosphate in patients with end-stage renal disease. *Drugs* 2009; 69: 2329–49.

Adverse Effects and Precautions

The most common adverse effects with lanthanum carbonate are gastrointestinal disturbances, including nausea, vomiting, constipation, diarrhoea, dyspepsia, and abdominal pain. There have been reports of gastrointestinal obstruction, ileus, and faecal impaction; tablets should be chewed thoroughly before swallowing. Caution is required when using lanthanum in patients with altered gastrointestinal anatomy or reduced gastrointestinal motility, including those taking medication that slows the digestive tract. Only small amounts of lanthanum are absorbed from the gastrointestinal tract but some accumulation of lanthanum in bone has been reported; the clinical significance of this is unknown.

Ingestion of lanthanum carbonate may produce a radio-opaque appearance on abdominal radiography.

Interactions

Lanthanum carbonate may increase gastric pH, reducing the absorption of other drugs such as chloroquine or ketoconazole which should be given at least 2 hours apart from lanthanum. Lanthanum carbonate releases lanthanum ions in the gastrointestinal tract, forming a complex with some drugs and reducing their absorption, see Antacids and Metal Ions under Ciprofloxacin, p. 265.1, and Chelators and Antidotes under Levothyroxine, p. 2342.1; tetracyclines may also be affected in this way.

Pharmacokinetics

Lanthanum carbonate is poorly absorbed from the gastrointestinal tract, with an absolute oral bioavailability of less than 1%. The small fraction that is absorbed is more than 99% bound to plasma proteins and is widely distributed in the tissues, particularly the bones, the liver, and the gastrointestinal tract. The plasma elimination half-life is reported to be about 36 hours in healthy subjects and 56 hours in those on dialysis. Lanthanum is excreted mainly in the faeces.

References.

1. Damment SJP, Pennick M. Clinical pharmacokinetics of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet* 2008; 47: 553–63.
2. Bronner F, *et al.* A model of the kinetics of lanthanum in human bone, using data collected during the clinical development of the phosphate binder lanthanum carbonate. *Clin Pharmacokinet* 2008; 47: 543–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Fosrenol; ***Austria***: Fosrenol; ***Belg.***: Fosrenol; ***Canad.***: Fosrenol; ***Cz.***: Fosrenol; ***Denm.***: Fosrenol; ***Fin.***: Fosrenol; ***Fr.***: Fosrenol; ***Ger.***: Fosrenol; ***Gr.***: Fosrenol; ***Hong Kong***: Fosrenol; ***Hung.***: Fosrenol; ***India***: Fosbait; Lanthonate; ***Indon.***: Fosrenol; ***Irl.***: Foznol; ***Israel***: Fosrenol; ***Ital.***: Foznol; ***Neth.***: Fosrenol; ***Norw.***: Fosrenol; ***Philipp.***: Fosrenol; ***Port.***: Fosrenol; ***S.Afr.***: Fosrenol; ***Spain***: Fosrenol; ***Swed.***: Fosrenol; ***Switz.***: Fosrenol; ***Thai.***: Fosrenol; ***UK***: Fosrenol; ***USA***: Fosrenol.

Lofexidine Hydrochloride

(BANM, USAN, rINNM)

Ba-168; Hidrocloruro de lofexidina; Lofeksidin Hidroklorür; Lofexidina, hidrocloruro de; Lofexidine, Chlorhydrate de; Lofexidini Hydrochloridum; MDL-14042; MDL-14042A; RMI-14042A; Лофексидина Гидрохлорид.

2-[1-(2,6-Dichlorophenoxy)ethyl]-2-imidazoline hydrochloride.

$C_{11}H_{17}Cl_2N_2O.HCl$=295.6
CAS — 31036-80-3 (lofexidine); 21498-08-8 (lofexidine hydrochloride).
ATC — N07BC04.
ATC Vet — QN07BC04.
UNII — V47G1SDI1B.

Pharmacopoeias. In *Chin.*

Uses and Administration

Lofexidine is an alpha$_2$-adrenoceptor agonist structurally related to clonidine (p. 1339.1). It has antihypertensive activity, but is used mainly in the control of opioid withdrawal symptoms.

In opioid withdrawal, lofexidine is given as the hydrochloride in an initial oral dose of 800 micrograms daily in divided doses. The dose may be increased gradually by 400 to 800 micrograms daily to a maximum of 2.4 mg daily; the maximum single dose should not exceed 800 micrograms. After 7 to 10 days, or longer in some cases, treatment is withdrawn gradually over at least 2 to 4 days.

Opioid dependence. The use of lofexidine has been reviewed.[1] A systematic review[2] of the use of alpha$_2$-adrenoceptor agonists in the management of opioid dependence (p. 109.2) concluded that they were as effective as methadone, although patients stayed in treatment for longer with methadone and there were fewer adverse effects with methadone than with clonidine. Lofexidine was associated with less hypotension than clonidine and may therefore be preferred, particularly for outpatient treatment.

1. Gish EC, *et al.* Lofexidine, an α_2-receptor agonist for opioid detoxification. *Ann Pharmacother* 2010; 44: 343–51.
2. Gowing L, *et al.* Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 (accessed 12/08/10).

Adverse Effects

Lofexidine has central alpha-adrenergic effects and may cause drowsiness, dizziness, dryness of the mouth, throat, and nose, hypotension, and bradycardia; prolongation of the QT interval has also been reported. Sedation may occur following overdosage.

Sudden withdrawal of lofexidine may produce rebound hypertension.

Precautions

Lofexidine should be used with caution in patients with cerebrovascular disease, cardiovascular disease including recent myocardial infarction, bradycardia, renal impairment, or a history of depression. It should be avoided in those at risk of QT prolongation.

It may cause drowsiness and if affected, patients should not drive or operate machinery.

Withdrawal of lofexidine therapy should be gradual over 2 to 4 days or more to reduce the risk of rebound hypertension.

Interactions

Lofexidine may enhance the central depressant effects of sedatives, including alcohol. It may also enhance the effects of antihypertensives. Lofexidine should not be used with other drugs which prolong the QT interval. Tricyclic antidepressants may reduce the efficacy of lofexidine.

Methadone. A 44-year-old opioid-dependent female receiving methadone had prolongation of the QT interval after a single 400-microgram dose of lofexidine.[1] The patient had previously had a normal QT while receiving methadone and it was suggested the effect might have been caused by the combination of the 2 drugs.

1. Schmittner J, *et al.* QT interval increased after single dose of lofexidine. *BMJ* 2004; 329: 1075.

Pharmacokinetics

Lofexidine is absorbed from the gastrointestinal tract and peak plasma concentrations occur after about 3 hours. It is extensively metabolised in the liver and excreted mainly in the urine. The elimination half-life is 11 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China:* Kai Er Ding (凯尔丁); *UK:* Britlofex.

Mesna (BAN, USAN, rINN)

D-7093; Mesnum; NSC-113891; UCB-3983; Mecha.
Sodium 2-mercaptoethanesulphonate.
$C_2H_5NaO_3S_2$=164.2
CAS — 19767-45-4.
ATC — R05CB05; V03AF01.
ATC Vet — QR05CB05; QV03AF01.
UNII — NR7O1405Q9.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mesna). A white or slightly yellow, hygroscopic, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. A 10% solution in water has a pH of 4.5 to 6.0. Store in airtight containers.

USP 36: (Mesna). A white or slightly yellow crystalline hygroscopic powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in cyclohexane. Store in airtight containers. pH 4.5 to 6.0.

Dimesna (rINN)

BNP-7787; Dimesnum; Mesna Disulfide; Димеска.
Disodium 2,2'-dithiodiethanesulfonate.
$C_4H_8Na_2O_6S_4$=326.3
CAS — 16208-51-8.
UNII — 230R951Y4D.

NOTE. The name Tavocept has been used as a trade mark for dimesna.

Incompatibility and stability. There was no evidence of degradation of mesna when stored in solution with ifosfamide in polyethylene infusion bags at room temperature for 7 hours[1] or in polypropylene syringes at room temperature or at 4 degrees for 4 weeks.[2] However, in the latter study ifosfamide concentrations fell by about 3% after 7 days and 12% after 4 weeks at both temperatures. Another study[3] found that mixtures of mesna with cyclophosphamide in polyethylene infusion bags were stable for 48 hours at 4 degrees and for 6 hours at room temperature.

Mesna has been reported to be incompatible with platinum compounds such as carboplatin and cisplatin.

1. Shaw IC, Rose JWP. Infusion of ifosphamide plus mesna. *Lancet* 1984; i: 1353–4.
2. Rowland CG, *et al.* Infusion of ifosfamide plus mesna. *Lancet* 1984; ii: 468.
3. Menard C, *et al.* Stability of cyclophosphamide and mesna admixtures in polyethylene infusion bags. *Ann Pharmacother* 2003; 37: 1789–92.

Uses and Administration

Mesna is used for the prevention of urothelial toxicity in patients being treated with the antineoplastics ifosfamide or cyclophosphamide. In the kidney, dimesna, the inactive metabolite of mesna, is reduced to free mesna. This has thiol groups that react with the metabolites of ifosfamide and cyclophosphamide, including acrolein, which are considered to be responsible for the toxic effects on the bladder.

The aim of mesna therapy is to ensure adequate levels of mesna in the urine throughout the period during which these toxic metabolites are present. The duration of mesna treatment should therefore equal that of the antineoplastic treatment plus the time taken for the concentration of antineoplastic metabolites in the urine to fall to non-toxic concentrations. Urinary output should be maintained and the urine monitored for haematuria and proteinuria throughout the treatment period. However, frequent emptying of the bladder should be avoided.

Mesna may be given intravenously or orally for the prevention of urothelial toxicity, the dosage and frequency depending on the antineoplastic regimen used. After oral use, availability of mesna in urine is about 50% of that after intravenous use and excretion in urine is delayed up to 2 hours and is more prolonged. The intravenous preparation may be given orally added to a flavoured drink; this mixture may be stored in a sealed container in a refrigerator for up to 24 hours. Alternatively, tablets are available.

Intravenous bolus antineoplastic regimens.

- If ifosfamide or cyclophosphamide is given as an intravenous bolus, the *intravenous dose of mesna* is 20% of the dose of the antineoplastic on a weight for weight basis given on 3 occasions over 15 to 30 minutes at intervals of 4 hours beginning at the same time as the antineoplastic injection; thus the total dose of mesna is equivalent to 60% of the antineoplastic given.
  This regimen is repeated each time the antineoplastic is used. Each individual dose of mesna may be increased to 40% of the dose of the antineoplastic and given 4 times at intervals of 3 hours in patients at high risk of urotoxicity; in such cases the total dose of mesna is equivalent to 160% of the antineoplastic given.
- The *oral dose of mesna* is 40% of the intravenous bolus dose of the antineoplastic given on 3 occasions at intervals of 4 hours beginning 2 hours before the antineoplastic injection; thus a total dose of mesna equivalent to 120% of the antineoplastic is given. In patients at high-risk of urothelial toxicity a shorter interval may be left between oral mesna doses, or the number of doses increased, or both.
- Alternatively, the initial dose of mesna (20% of the dose of the antineoplastic) may be given *intravenously* at the same time as the antineoplastic, followed by two *oral doses* (each 40% of the dose of the antineoplastic) given 2 and 6 hours after the intravenous dose.

Any of these regimens may be used if **cyclophosphamide** is given **orally.**

Intravenous infusion antineoplastic regimens.

- If the antineoplastic is given as a continuous intravenous infusion, an initial bolus intravenous injection of mesna (20% of the first 24-hour antineoplastic dose) is given at the start of the antineoplastic regimen, followed by a continuous infusion of mesna given concurrently with the antineoplastic infusion at the same total dose (100%). A further 12-hour infusion of mesna (60% of the final 24-hour antineoplastic dose) is started when the antineoplastic regimen finishes; thus a total dose of mesna equivalent to 180% of the antineoplastic dose is given.
  The final 12-hour infusion may be replaced either by 3 intravenous injections each of 20% of the final 24-hour antineoplastic dose at intervals of 4 hours, the first injection being given 4 hours after the infusion has been stopped, or by *oral mesna* given in 3 doses each of 40% of the final 24-hour antineoplastic dose, the first dose being given when the infusion is stopped, and the second and third doses being given 2 and 6 hours later.

Mesna has also been used as a **mucolytic** in the management of some respiratory-tract disorders. A dose of 600 mg to 1.2 g is inhaled up to 4 times daily via a nebuliser; the drug may also be given by direct endotracheal instillation in a dose of 200 to 400 mg/hour. For sinusitis, 400 to 600 mg can be instilled into the sinuses and repeated every 2 or 3 days if needed.

For doses in children, see below.

Dimesna is under investigation as an antineoplastic and a chemoprotectant.

General references.

1. Schoenike SE, Dana WJ. Ifosfamide and mesna. *Clin Pharm* 1990; 9: 179–91.
2. Siu LL, Moore MJ. Use of mesna to prevent ifosfamide-induced urotoxicity. *Support Care Cancer* 1998; 6: 144–54.
3. Hensley ML, *et al.* American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol* 2009; 27: 127–45. Also available at: http://jco.ascopubs.org/cgi/reprint/27/1/127.pdf (accessed 15/01/10)

Administration in children. Mesna is used for the prevention of urothelial toxicity in children being treated with the antineoplastics ifosfamide and cyclophosphamide. Doses are similar to those used in adults (see above), although it may be necessary to use a more intensive dose schedule as children generally micturate more frequently than adults. Some parenteral formulations of mesna contain the preservative benzyl alcohol which has been associated with a fatal toxic syndrome in neonates and infants, see Neonates, under Benzyl Alcohol, p. 1740.1. Such formulations should not be used in children aged 12 years of age or less.

Mesna has also been used as a mucolytic in children with cystic fibrosis. Although unlicensed for such use in the UK, the *BNFC* suggests 3 to 6 mL of a 20% solution of mesna, nebulised twice daily.

Hyperhomocysteinaemia. Mesna has been tried for hyperhomocysteinaemia, implicated in the pathogenesis of some cardiovascular diseases (see Atherosclerosis, p. 1250.2, and Ischaemic Heart Disease, p. 1254.2, Venous Thrombosis, p. 1274.1, and Stroke, p. 1269.2), with variable results.[1,2]

1. Urquhart BL, *et al.* Mesna as a nonvitamin intervention to lower plasma total homocysteine concentration: implications for assessment of the homocysteine theory of atherosclerosis. *J Clin Pharmacol* 2007; 47: 991–7.
2. Urquhart BL, *et al.* Mesna for treatment of hyperhomocysteinemia in hemodialysis patients: a placebo-controlled, double-blind, randomized trial. *Clin J Am Soc Nephrol* 2008; 3: 1041–7.

Adverse Effects and Precautions

Adverse effects that may occur after use of mesna include gastrointestinal disturbances, headache, fatigue, depression, irritability, hypotension (but see p. 1558.1), tachycardia, rash, musculoskeletal pain, hyperaesthesia, rhinitis, pharyngitis, cough, flu-like symptoms, injection-site reactions, flushing, dizziness, and drowsiness. Bronchospasm has been reported after nebulisation and endotracheal use.

Hypersensitivity or pseudo-hypersensitivity reactions have been reported rarely, and include skin and mucous membrane reactions, a transient rise in liver enzyme values, thrombocytopenia, and general symptoms such as fever;

sudden hypotension and tachycardia occasionally occur. Such reactions appear to be more common in patients with auto-immune disorders.

Mesna may produce a false positive result in diagnostic tests for urinary ketones and may produce a false positive or false negative result in diagnostic tests for urinary erythrocytes.

Some parenteral formulations of mesna contain the preservative benzyl alcohol which has been associated with a fatal toxic syndrome in neonates and infants, see Neonates, under Benzyl Alcohol, p. 1740.1. Such formulations should not be used in children aged 12 years of age or less.

Effects on blood pressure. Hypotension may occur with mesna; however, severe hypertension has also been reported[1] after use of mesna, either alone or with ifosfamide.

1. Gilleece MH, Davies JM. Mesna therapy and hypertension. *DICP Ann Pharmacother* 1991; 25: 867.

Effects on the nervous system. For reports of severe encephalopathy in patients receiving mesna and ifosfamide, see p. 806.3.

Hypersensitivity. Hypersensitivity reactions including rash, fever, nausea, facial and periorbital oedema, ulceration of mucous membranes, and tachycardia have been attributed to mesna.[1-4] Reactions may be more common in patients with auto-immune disorders; drug eruptions developed in 7 of 16 patients receiving mesna and cyclophosphamide for auto-immune disorders.[5] Five of these patients had a rash, with angioedema in 2 cases, and a pseudo-hypersensitivity reaction was diagnosed.

1. Lang E, Goos M. Hypersensitivity to mesna. *Lancet* 1985; ii: 329.
2. Seidel A, *et al.* Allergic reactions to mesna. *Lancet* 1991; 338: 381.
3. Gross WL, *et al.* Allergic reactions to mesna. *Lancet* 1991; 338: 381–2.
4. D'Cruz D, *et al.* Allergic reactions to mesna. *Lancet* 1991; 338: 705–6.
5. Zonzits E, *et al.* Drug eruptions from mesna: after cyclophosphamide treatment of patients with systemic lupus erythematosus and dermatomyositis. *Arch Dermatol* 1992; 128: 80–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mesna as probably not porphyrinogenic when used for the prevention of urothelial toxicity in patients given antineoplastics; it may be used as a drug of first choice and no precautions are needed. When used as a mucolytic, mesna is not classified.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Pharmacokinetics

Mesna is absorbed from the gastrointestinal tract. It is rapidly metabolised to the disulfide, dimesna, after oral or intravenous dosage and is excreted in the urine as both metabolite and unchanged drug; dimesna is reduced back to mesna, which is the active form, in the kidney. After an intravenous dose the half-lives of mesna and dimesna are reported to be about 20 minutes and 70 minutes, respectively, but after repeated dosing (intravenous followed by oral) the half-life of mesna is reported to be up to 8 hours. Mesna is about 70% bound to plasma proteins.

References.

1. Burkert R, *et al.* Bioavailability of orally administered mesna. *Arzneimittelforschung* 1984; 34: 1597–1600.
2. James CA, *et al.* Pharmacokinetics of intravenous and oral sodium 2-mercaptoethane sulphonate (mesna) in normal subjects. *Br J Clin Pharmacol* 1987; 23: 561–8.
3. El-Yazigi A, *et al.* Pharmacokinetics of mesna and dimesna after simultaneous intravenous bolus and infusion administration in patients undergoing bone marrow transplantation. *J Clin Pharmacol* 1997; 37: 618–24.
4. Verschraegen M, *et al.* Pharmacokinetics of BNP7787 and its metabolite mesna in plasma and ascites: a case report. *Cancer Chemother Pharmacol* 2003; 51: 525–9.
5. Boven E, *et al.* Phase I and pharmacokinetic study of the novel chemoprotector BNP7787 in combination with cisplatin and attempt to eliminate the hydration schedule. *Br J Cancer* 2005; 92: 1636–43.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Delinar†; Mestian; Neper; Varimesna; *Austral.*: Uromitexan; *Austria*: Mistabron†; Uromitexan; *Belg.*: Mistabron; Uromitexan; *Braz.*: Mitexan; Tevamesna; *Canad.*: Uromitexan; *Chile*: Mucofluid†; Uromitexan; Uroprot; *China*: Mei An (美安); Uromitexan (优美善); *Cz.*: Mistabron; Uromitexan; *Denm.*: Uromitexan; *Fin.*: Uromitexan; *Fr.*: Mucofluid†; Uromitexan; *Ger.*: Uromitexan; *Gr.*: Mucofluid; Uromitexan; *Hong Kong*: Mistabron†; Uromitexan; *Hung.*: Uromitexan; *India*: Mistabron; Uromitexan; *Indon.*: Uromitexan; *Irl.*: Uromitexan; *Israel*: Mexan†; *Ital.*: Uromitexan; *Jpn*: Uromitexan; *Mex.*: Mescryo; Mesnil; Mesodal; Uromes; Uroprot; Ziken†; *Neth.*: Mistabron†; Uromitexan; *Norw.*: Uromitexan; *NZ*: Uromitexan; *Philipp.*: Mistabron; Uromitexan†; *Pol.*: Anti-Uron; Mistabron†; Mucofluid; Uromitexan; *Port.*: Uromitexan; *Rus.*: Uromitexan (Уромитексан); *S.Afr.*: Mistabron; Uromitexan; *Singapore*: Mistabron†; Uromitexan; *Spain*: Mucofluid; Uromitexan; *Swed.*: Uromitexan; *Switz.*: Uromitexan; *Thai.*: Uromitexan; Uroprot; *Turk.*: Uromitexan; *USA*: Mesnex.

Multi-ingredient Preparations. *India*: Holoxan Uromitexan; Ifex-M; Ifomid-M; Ifoxan with Mesna; Ipamide with Mesna†; Isoxan.

Methionine *(BAN, USAN, rINN)*

L-Metionina; M; Methionin; L-Methionine; Méthionine; S-Methionine; Methioninum; Metioniini; Metionin; Metionín; Metionina; Metioninas; Metiyonin; Метионин; Метіонін.

L-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$=149.2

CAS — 63-68-3.

ATC — V03AB26.

ATC Vet — QA05BA90; QG04BA90; QV03AB26.

UNII — AE28F7PNPL

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methionine). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very slightly soluble in alcohol. A 2.5% solution in water has a pH of 5.5 to 6.5. Protect from light.

USP 36: (Methionine). White crystals having a characteristic odour. Soluble in water, in warm dilute alcohol, and in dilute mineral acids; insoluble in dehydrated alcohol, in acetone, in ether, and in benzene. pH of a 1% solution in water is between 5.6 and 6.1.

DL-Methionine

Methionin racemický; DL-Méthionine; DL-Methioninum; Methioninum Racemicum; DL-Metioniini; DL-Metionin; DL-Metionina; DL-Metioninas; Racemethionine (USAN); DL-Метионин.

DL-2-Amino-4-(methylthio)butyric acid.

$C_5H_{11}NO_2S$=149.2

CAS — 59-51-8.

ATC — V03AB26.

ATC Vet — QV03AB26.

UNII — 73JWT2K6T3.

NOTE. The name methionine is often applied to DL-methionine.

Compounded preparations of DL-methionine may be represented by the following names:

- Co-methiamol *x/y* (*BAN*)—where *x* and *y* are the strengths in milligrams of DL-methionine and paracetamol respectively.

Pharmacopoeias. In *Eur.* (see p. vii), Also in *USNF*. *Int.*, and *Viet.*

Ph. Eur. 8: (DL-Methionine). An almost white crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol; dissolves in dilute acids and in dilute solutions of alkali hydroxides. A 2% solution in water has a pH of 5.4 to 6.1. Protect from light.

USNF 31: (Racemethionine). An almost white, crystalline powder or small flakes. Sparingly soluble in water; very slightly soluble in alcohol. It dissolves in dilute acids and in dilute solutions of alkali hydroxides. pH of a 2% solution in water is 5.4 to 6.1. Protect from light.

Uses and Administration

L-Methionine is an essential amino acid that is included in oral dietary supplements and amino-acid solutions used for parenteral nutrition (p. 2044.1). It enhances the synthesis of glutathione and has been used as an alternative to acetylcysteine in the treatment of paracetamol poisoning to prevent hepatotoxicity; however, the use of methionine as an antidote has been largely superseded by acetylcysteine (see p. 116.2). It also lowers urinary pH and is used as an adjunct in the management of urinary-tract infections, to treat renal calculi, and to reduce irritation of the skin caused by urine. Methionine is also used as an adjunct in the treatment of liver disorders, and high oral doses have been given as a loading test in the assessment of hyperhomocysteinaemia (below).

The literature relating to the use of methionine in paracetamol poisoning is, in general, imprecise as to the form of methionine used. In the UK, the usual dose of methionine is 2.5 g orally every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. For doses in children, see below. Preparations containing both methionine and paracetamol have been formulated for use in situations where overdosage may occur.

To lower the urinary pH during chronic urinary-tract infections or to treat renal calculi, a usual oral dose of L-methionine 0.5 to 1 g is given 3 times daily.

Acetylmethionine has also been used.

Administration in children. Methionine is included in amino-acid solutions used for parenteral nutrition in children; it has also been used as an antidote in the treatment of paracetamol poisoning, but has been largely superseded by acetylcysteine.

For paracetamol overdose, children under 6 years of age can be given an oral dose of 1 g methionine every 4 hours for 4 doses starting less than 10 to 12 hours after ingestion of the paracetamol. Children aged 6 years or over can be given the adult dose, see above.

Hyperhomocysteinaemia. Methionine is metabolised to homocysteine and an oral methionine-loading test is used in the assessment of hyperhomocysteinaemia which has been implicated in the development of several disorders including cardiovascular disease (see p. 2063.3) and psychiatric conditions such as Alzheimer's disease and depression (see p. 2046.3). Although fasting homocysteine measurements can be used to diagnosis hyperhomocysteinaemia, about half of patients have normal fasting homocysteine but an elevated concentration after a methionine-loading test,[1] which could indicate vitamin B_6 deficiency or a genetic mutation in the enzyme involved in the metabolism of homocysteine.[2] An oral dose of L-methionine 100 mg/kg is given and plasma homocysteine concentrations measured about 6 hours post-dose.[1,2]

1. van der Griend R, *et al.* Postmethionine-load homocysteine determination for the diagnosis hyperhomocysteinaemia and efficacy of homocysteine lowering treatment regimens. *Vasc Med* 2002; 7: 29–33.
2. Herrmann W, *et al.* Hyperhomocysteinaemia: a critical review of old and new aspects. *Curr Drug Metab* 2007; 8: 17–31.

Adverse Effects and Precautions

Methionine may cause nausea, vomiting, drowsiness, and irritability. Methionine can cause acidification of the urine and blood. It should not be used in patients with acidosis, hyperuricaemia or hyperuricosuria, uric acid- or cystine-containing renal calculi, or metabolic disorders such as oxalosis, homocystinuria, or hypermethioninaemia. Methionine may aggravate hepatic encephalopathy in patients with established liver damage; it should be used with caution in patients with severe liver disease.

High-dose regimens. High doses of oral methionine (5 to 40 g daily for up to 2 months) have precipitated psychotic symptoms in schizophrenic patients, although doses of 10 g have been given to healthy subjects without significant adverse effects. Dizziness, drowsiness, polyuria, and changes in blood pressure were reported in a controlled study of patients with cardiovascular disease given the methionine-loading test (see Hyperhomocysteinaemia, above). A fatality has been reported after a methionine-loading test in which the subject was thought to have been given about 10 times the intended dose.

Methionine is metabolised to homocysteine, high levels of which have been associated with cardiovascular disease (see p. 2063.3) and psychiatric conditions such as Alzheimer's disease and depression (see p. 2046.3). There is no evidence to suggest that dietary intake of methionine causes vascular damage, and although the high doses used in the methionine-loading test result in endothelial dysfunction, this effect is acute and so a single test is therefore deemed unlikely to be harmful.[1]

1. Garlick PJ. Toxicity of methionine in humans. *J Nutr* 2006; 136 (suppl 6): 1722S–1725S.

Interactions

Methionine may be adsorbed by activated charcoal and the effect of oral methionine may be reduced if they are given together. Methionine is an urinary acidifier and may increase exposure to drugs that undergo tubular reabsorption in acidic urine, such as some antibacterials.

Dopaminergics. For reference to the antagonism of the antiparkinsonian effect of *levodopa* by methionine, see Nutritional Agents, under Interactions of Levodopa, p. 907.3.

Pharmacokinetics

Methionine is well absorbed from the gastrointestinal tract. It is metabolised in the liver to *S*-adenosylmethionine (ademetionine, p. 2429.3) and then homocysteine. Homocysteine is then either remethylated to methionine or forms taurine and cysteine (a precursor of glutathione). Methionine has a half-life of about 1 to 1.5 hours. About 5 to 10% of a dose is excreted unchanged in the urine and about 80% is excreted as an inorganic sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Methnine†; *Austria*: Acimethin; *China*: Bai Fu Li (百扶力); Qi Cun (齐存); Xin Yuan

Da (欣源达); *Ger.*: Acimethin†; Acimol; Methiotrans†; Urol methin; *Gr.*: Urosamine; *Rus.*: Eslidine (Эслидин); *Switz.*: Acimethin; *USA*: M-Caps; Uracid.

Multi-ingredient Preparations. *Arg.*: Cistidac; Cistimax; Dial-ND; Gastricur; Levantol Procaina; Piel Vital; Tricomax; Triconal; Valcatil Max; Valcatil Plus; Valcatil; *Austral.*: Berberis Complex†; PM Syrin; *Braz.*: Abcler; Anekron; Biohepax†; Chofrafig; Enterofigon; Epativan; Epocler; Extrato Hepatico Composto; Hepalin; Hepatox; Lisotox; Metiocolin B12; Metiocolin Composto; Necro B6; Panvitrop; Regenom; Silimalon; Xantinon B12; Xantinon Complex; *Canad.*: Betagard; Emulsi Factors; Formula AO†; Formula IC†; Formula VIR†; Hepaticol; Right Choice PM†; *Chile*: Vantux Plus; Vantux; *China*: Bao Jia Wei (保甲维); Bei Xin (倍辛); Bo Shi Duo An (博仕多安); Fu Er Jian (孚尔健); Gan Du Xin (甘度欣); Neo-Minophagen C (美能); Tian Qi (天芪); Wei Bi Lai (维必莱); Wei Ding Xi (维定喜); Wei Li (维力)); Xi Bi Kang (西比康); Yi Wei (异维); *Fr.*: Anacaps tri-Activ; Anacaps†; Forcapil; Lobamine-Cysteine; Nivabetol†; Verrulyse-Methionine; *Ger.*: Merz Spezial Dragees N†; *Hong Kong*: Lipochol; Pilfood; Revicon; Super Vita Vim; *Hung.*: Forcapil; Revalid; *India*: Alnacer; Beminal; Delage; Dexia; Enerjex; Revastin Plus; Fibrotin; Furtipil-L; Gardian; Inpro; Livobion; Livobion; Lycostar-CM; Namsafe; Neutrosec; Pamela; Parasafe; *Indon.*: BIO-EPL†; Carni Plus; DFM; Lipagent; Methicol; Methioson; Vionin NF; Vionin; *Irl.*: Antox; *Ital.*: Biomineral One; Biomineral Plus; Biophase Complex†; Chiton; Detoxicon; Lipoenergy; Vitreolux; *Malaysia*: Revicon; Revital; *Mex.*: Lipovitasi-Or; *Philipp.*: ALAnerv; Arcostrong†; Biomix; Energel; Rejuvenex; Revicon Forte (Improved); *Pol.*: Methiovit†; Revalid; *Rus.*: Decamevit (Декамевит); Remaxol (Ремаксол); Selmevit (Семевит); *S.Afr.*: Hepavite†; *Singapore*: Revicon; Vitiron; *Spain*: Dertrase; Epitelizante; *Switz.*: Mechovit†; Vitiron; *Thai.*: Lipochol; Liporon; Revicon†; Vita Multicap; Vitop; *UK*: Antox; Lipotropic Factors; Paradote†; Pilfood; *Ukr.*: Decamevit (Декамевит); Detoxil (Детоксил); Hepahealth (Гепахелс); PM Sirin (ПМ Сирин); Quadevit (Квадевит); Revalid (Ревалид); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Amino-Cerv; Geritol; Liponol; Methatropic.

Methylthioninium Chloride

(BAN, rINN)

Azul de Metileno; Bleu de Méthylène; Błękit metylenowy; Blu di Metilene; CI Basic Blue 9; Cloruro de metiltioninio; Colour Index No. 52015; Methyleenblauw; Methylenblåt; Methylenblau; Methylene Blue; Methylenii Caeruleum; Methylthioninii Chloridum; Methylthioninii Chloridum Hydricum; Méthylthioninium, Chlorure de; Methylthioninniumchlorid; Methylthioninium-chlorid hydrát; Metilen Mavisi; Metiltioninio cloridas; Metiltioninio Clorure; Metiltioninio, cloruro de; Metiltionin-klorid; Metyleenisininen; Metylenblått; Metylenblått; Metylotioniowy chlorek; Metyltioniniumklorid; Metyylitioniniumkloridi; Schultz No. 1038; Tetramethylthionine Chloride Trihydrate; Метилтионина Хлорид; Метиленовый Синий; Метиленовий Синій.

3,7-Bis(dimethylamino)phenazathionium chloride trihydrate.

$C_{16}H_{18}ClN_3S,3H_2O$=373.9

CAS — 61-73-4 (anhydrous methylthioninium chloride); 7220-79-3 (methylthioninium chloride trihydrate).

ATC — V03AB17; V04CG05.

ATC Vet — QV03AB17; QV04CG05.

UNII — T42P99266K (methylthioninium chloride trihydrate); 8NAP7826UB (anhydrous methylthioninium chloride).

NOTE. *Commercial methylthioninium chloride may consist of the double chloride of tetramethylthionine and zinc, and is not suitable for medicinal use.*

The name Rember has been used as a trade mark for methylthioninium chloride.

Pharmacopoeias. In *Chin.* and *US*; in *Eur.* (see p. vii) (as xH_2O); in *Int.* (as anhydrous or $3H_2O$).

Ph. Eur. 8: (Methylthioninium Chloride). A dark blue, crystalline powder with a copper-coloured sheen, or green crystals with a bronze-coloured sheen. Soluble in water; slightly soluble in alcohol. Store in airtight containers. Protect from light.

USP 36: (Methylene Blue). Dark green crystals or crystalline powder with a bronze-like lustre. Is odourless or practically so. Solutions in water or alcohol are deep blue in colour. Soluble 1 in 25 of water and 1 in 65 of alcohol; soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Methylthioninium chloride is a thiazine dye that is used in the treatment of methaemoglobinaemia. It is also used as an antiseptic, as a bacteriological stain, as a dye in diagnostic procedures or surgery, to prevent urolithiasis, and for viral photoinactivation in some plasma products.

Methylthioninium chloride is given intravenously or orally. The 1% solution for injection can be given orally after dilution; 5 to 10 mL is diluted in 100 to 200 mL of water. It can also be applied topically; the blue colour can be removed from the skin with hypochlorite solution.

In patients with methaemoglobinaemia, therapeutic doses of methylthioninium chloride can lower the levels of methaemoglobin in the red blood cells. It activates a normally dormant reductase enzyme system, which reduces the methylthioninium chloride to leucomethylene blue that in turn is able to reduce methaemoglobin to haemoglobin. However, in large doses methylthioninium chloride can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency and is potentially harmful (see p. 1560.2).

In the treatment of acute methaemoglobinaemia, such as in nitrite poisoning, methylthioninium chloride is given intravenously as a 1% solution in doses of 1 to 2 mg/kg injected over several minutes. A repeat dose may be given after 30 to 60 minutes if required. A maximum total dose of 7 mg/kg has been suggested. Doses are calculated from lean body-weight. It may also be used for the maintenance of chronic or inherited methaemoglobinaemia in oral doses of up to 300 mg daily.

When methylthioninium chloride is used as a diagnostic aid for fistula detection, 1 to 3 mL of a 1% solution is injected into the opening and the appearance of blue discoloration in the surrounding tissues noted. Similar or more dilute solutions have been used to aid sentinel lymph-node biopsy (see below). To stain the parathyroid glands, a dose of 5 mg/kg is diluted in 500 mL of sodium chloride 0.9% or glucose 5% and infused intravenously over 1 hour.

Methylthioninium chloride has a mildly antiseptic action and has been given orally in minor urinary-tract infections and to prevent urolithiasis. It is also included in some preparations intended for application to the eye, mouth and pharynx, and skin.

Methylthioninium chloride has been used in the diagnosis of ruptured amniotic membranes (but see Pregnancy under Adverse Effects and Precautions, p. 1560.3). It was formerly used in a renal-function test.

Administration in children. Methylthioninium chloride is used in children for the treatment of methaemoglobinaemia in the same doses as adults, see Uses and Administration, above. It has been suggested that the metabolism of methylthioninium chloride to leucomethylene blue is likely to be less efficient in neonates, and some countries do not recommend use in infants under 4 months of age.

Dementia. The aggregation of tau protein filaments in the brain is believed to be associated with the development of cognitive symptoms in Alzheimer's disease (see Dementia, p. 388.1). Methylthioninium chloride, which is thought to dissolve and prevent such aggregations, is under investigation in the management of Alzheimer's disease.

References.
1. Oz M, *et al.* Methylene blue and Alzheimer's disease. *Biochem Pharmacol* 2009; 78: 927–32.

Glutaric aciduria. Glutaric aciduria type II is a metabolic disorder associated with a deficiency of electron-transferring flavoproteins involved in the metabolism of amino acids and fatty acids. Treatment may involve diets low in fats and protein, and some success has been reported with riboflavin. Methylthioninium chloride may also be of benefit since it may act as an electron acceptor, and a response has been seen in an infant[1] with neonatal glutaric aciduria type II. An association has also been noted between encephalopathy due to ifosfamide neurotoxicity (see Effects on the Nervous System under Adverse Effects of Ifosfamide, p. 806.3) and glutaric aciduria, possibly due to inhibition of electron transport by a metabolite of ifosfamide. Methylthioninium chloride has therefore been tried for both treatment and prevention of ifosfamide neurotoxicity; however, conflicting results have been reported[2-6] and its role remains unclear.[7]

1. Harpey J-P, *et al.* Methylene-blue for riboflavine-unresponsive glutaricaciduria type II. *Lancet* 1986; i: 391.
2. Küpfer A, *et al.* Prophylaxis and reversal of ifosfamide encephalopathy with methylene-blue. *Lancet* 1994; 343: 763–4.
3. Zulian GB, *et al.* Methylene blue for ifosfamide-associated encephalopathy. *N Engl J Med* 1995; 332: 1239–40.
4. Pelgrims J, *et al.* Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer* 2000; 82: 291–4.
5. Brunello A, *et al.* Ifosfamide-related encephalopathy in elderly patients: report of five cases and review of the literature. *Drugs Aging* 2007; 24: 967–73.
6. Sweiss KI, *et al.* Encephalopathy after high-dose ifosfamide: a retrospective cohort study and review of the literature. *Drug Safety* 2008; 31: 989–96.
7. Patel PN. Methylene blue for management of ifosfamide-induced encephalopathy. *Ann Pharmacother* 2006; 40: 299–303.

Hypotension. Excess nitric oxide production leading to peripheral vasodilatation may be involved in the pathogenesis of hypotension associated with several conditions and it has been suggested that methylthioninium chloride, which is a guanylate cyclase inhibitor, may block the effects of nitric oxide and increase blood pressure in such cases. Studies[1,2] in patients with septic shock, including 5 neonates[3] with refractory hypotension assumed to be due to sepsis, have suggested that methylthioninium chloride increases blood pressure and improves tissue oxygenation, although no mortality benefit has been found. A subsequent systematic review[4] noted that although there was evidence of improvement in haemodynamic parameters it was mainly from observational studies, and that there was a risk of worsening respiratory function. If such treatment were to be used, an initial intravenous bolus dose of 2 mg/kg was probably appropriate.

There have also been reports of the successful use of methylthioninium chloride in patients with anaphylactic shock,[5] hypotension associated with haemodialysis,[6] vasoplegia after cardiac surgery,[7] and severe hepatopulmonary syndrome,[8] all of which may involve increased nitric oxide production. However, the role of methylthioninium chloride in these conditions is not established.[9]

The usual management of shock is discussed on p. 1279.3; anaphylactic shock should be treated with adrenaline, as discussed on p. 1293.2.

1. Preiser J-C, *et al.* Methylene blue administration in septic shock: a clinical trial. *Crit Care Med* 1995; 23: 259–64.
2. Kirov MY, *et al.* Infusion of methylene blue in human septic shock: a pilot, randomized, controlled study. *Crit Care Med* 2001; 29: 1860–7.
3. Driscoll W, *et al.* Effect of methylene blue on refractory neonatal hypotension. *J Pediatr* 1996; 129: 904–8.
4. Paciullo CA, *et al.* Methylene blue for the treatment of septic shock. *Pharmacotherapy* 2010; 30: 702–15.
5. Oliviera Neto AM, *et al.* Methylene blue: an effective treatment for contrast medium-induced anaphylaxis. *Med Sci Monit* 2003; 9: CS102–CS106.
6. Peer G, *et al.* Methylene blue, a nitric oxide inhibitor, prevents haemodialysis hypotension. *Nephrol Dial Transplant* 2001; 16: 1436–41.
7. Levin RL, *et al.* Methylene blue reduces mortality and morbidity in vasoplegic patients after cardiac surgery. *Ann Thorac Surg* 2004; 77: 496–9.
8. Schenk P, *et al.* Methylene blue improves the hepatopulmonary syndrome. *Ann Intern Med* 2000; 133: 701–6.
9. Stawicki SP, *et al.* Methylene blue and vasoplegia: who, when, and how? *Mini Rev Med Chem* 2008; 8: 472–90.

Ifosfamide encephalopathy. See Glutaric Aciduria, above.

Lymph node biopsy. Methylthioninium chloride is used as an alternative to other blue dyes as an adjunct in the identification and biopsy of sentinel lymph nodes in cancer patients, particularly in breast cancer[1-4] but also in those with gastrointestinal tumours,[5] or malignant melanoma.[6]

Typically, the dye has been injected as up to 5 mL of a 1% solution, but in breast cancer patients infiltration into the subareolar area of a more dilute solution, such as a 0.125% solution is effective and may be associated with fewer complications.[2,3] (For mention of necrosis associated with use in sentinel node biopsy see p. 1560.3.)

1. Masannat Y, *et al.* Properties and characteristics of the dyes injected to assist axillary sentinel node localization in breast surgery. *Eur J Surg Oncol* 2006; 32: 381–4.
2. Zakaria S, *et al.* Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. *Am J Surg* 2008; 196: 228–33.
3. Mathelin C, *et al.* Methylene blue dye, an accurate dye for sentinel lymph node identification in early breast cancer. *Anticancer Res* 2009; 29: 4119–25.
4. East JM, *et al.* Sentinel lymph node biopsy for breast cancer using methylene blue dye manifests a short learning curve among experienced surgeons: a prospective tabular cumulative sum (CUSUM) analysis. *BMC Surg* 2009; 9: 2.
5. Soni M, *et al.* A prospective trial comparing 1% lymphazurin vs 1% methylene blue in sentinel lymph node mapping of gastrointestinal tumors. *Ann Surg Oncol* 2009; 16: 2224–30.
6. Liu Y, *et al.* A randomized study comparing the effectiveness of methylene blue dye with lymphazurin blue dye in sentinel lymph node biopsy for the treatment of cutaneous melanoma. *Ann Surg Oncol* 2008; 15: 2412–17.

Methaemoglobinaemia. Methaemoglobinaemia is a rare disorder of the blood in which there is an increase in the proportion of haemoglobin present in the oxidised form. Inherited methaemoglobinaemia may be due either to a deficiency of methaemoglobin reductase or to a structural abnormality of haemoglobin.[1] Acquired methaemoglobinaemia may be caused by drugs[1,2] or chemicals that oxidise haemoglobin, including nitrates and nitrites, sodium nitroprusside, dapsone, sulfonamides, phenacetin, and some local anaesthetics such as prilocaine; it may occur as a result of direct administration or occupational[3] or environmental exposure. Exposure to low doses over long periods may lead to chronic methaemoglobinaemia whereas large doses may lead to an acute effect.

Methaemoglobinaemia has a profound effect on oxygen transport by the blood; there is an increase in oxygen affinity leading to reduced tissue delivery and varying degrees of cyanosis. The presence of symptoms depends upon the degree and rapidity of methaemoglobin formation. Chronic mild methaemoglobinaemia is generally well tolerated although patients may appear cyanotic. Acute methaemoglobinaemia, particularly where methaemoglobin levels exceed 20%, is associated with dyspnoea, headache, malaise, giddiness, and altered mental state; methaemoglobin levels above 50% may lead to vascular collapse, coma, and death.

Patients with inherited methaemoglobinaemia are usually asymptomatic but treatment may be given for cosmetic purposes to reduce the cyanotic skin colour. Patients with reductase deficiency generally respond to oral therapy with drugs that promote the reduction of methaemoglobin to haemoglobin, such as ascorbic acid, riboflavin, or methylthioninium chloride; methylthioninium chloride may also be given intravenously. Patients with structural abnormalities of haemoglobin do not respond. In acquired methaemoglobinaemia the causative agent should be identified and removed. Chronic or mild cases may not require treatment but acute symptomatic methaemoglobinaemia may be life-threatening and patients should be given intravenous methylthioninium chloride, along with oxygen and other supportive therapy as required. Toxicity is uncommon with methylthioninium chloride but it should not be used for methaemoglobinaemia due to the use of nitrites for cyanide poisoning since increased toxicity may result (for debate about its use after chlorate poisoning, see Adverse Effects and Precautions, below). Severe methaemoglobinaemia may require exchange transfusion; exchange transfusion with haemodialysis is the treatment of choice in patients with acute methaemoglobinaemia and haemolysis. Hyperbaric oxygen therapy has also been suggested in severe cases. Ascorbic acid is not useful in the acute situation since it acts too slowly but it may be of benefit where maintenance therapy is required.

1. do Nascimento TS, *et al.* Methemoglobinemia: from diagnosis to treatment. *Rev Bras Anestesiol* 2008; 58: 657–64.
2. Coleman MD, Coleman NA. Drug-induced methaemoglobinaemia: treatment issues. *Drug Safety* 1996; 14: 394–405.
3. Bradberry SM. Occupational methaemoglobinaemia: mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev* 2003; 22: 13–27.

ADMINISTRATION. In acute methaemoglobinaemia, methylthioninium chloride is usually given by intravenous bolus injection, but repeated doses may be needed and continuous intravenous infusion has also been used. Methylthioninium chloride was given at a dose of 7.5 to 10 mg/hour for 43 hours to control methaemoglobinaemia after dapsone poisoning.[1] The patient had responded to two bolus doses of 100 mg but methaemoglobinaemia had subsequently increased again owing to the long half-life of dapsone. Additional therapy included repeated doses of activated charcoal. A dosing schedule for methylthioninium chloride of 1 to 2 mg/kg as a bolus followed by a continuous infusion at an initial rate of 100 to 150 micrograms/kg per hour was suggested. Others have found that continuous infusion of methylthioninium chloride was more effective than intermittent infusion in a small number of children with dapsone-induced methaemoglobinaemia.[2]

Methylthioninium chloride has also been given successfully by intraosseous infusion for acute methaemoglobinaemia in an infant in whom attempted intravenous access failed.[3]

1. Dawson AR, Whyte IM. Management of dapsone poisoning complicated by methaemoglobinaemia. *Med Toxicol Adverse Drug Exp* 1989; 4: 387–92.
2. Prasad R, *et al.* Dapsone induced methemoglobinemia: intermittent vs continuous intravenous methylene blue therapy. *Indian J Pediatr* 2008; 75: 245–7.
3. Herman ML, *et al.* Methylene blue by intraosseous infusion for methemoglobinemia. *Ann Emerg Med* 1999; 33: 111–13.

Photodynamic therapy. Methylthioninium chloride is a photosensitiser and, as well as being used for bacterial, fungal, and viral photoinactivation,[1] has also been tried in photodynamic therapy (PDT) for various refractory conditions. It has been applied topically for PDT of oral lichen planus,[2,3] plaque psoriasis,[4] acne vulgaris,[5] and herpes simplex.[6] It has also been injected into lesions for PDT of Kaposi's sarcoma[7] (for further discussion of PDT and its use in malignancy, see p. 849.1).

1. Biel MA. Photodynamic therapy of bacterial and fungal biofilm infections. *Methods Mol Biol* 2010; 635: 175–94.
2. Aghahosseini F, *et al.* Treatment of oral lichen planus with photodynamic therapy mediated methylene blue: a case report. *Med Oral Patol Oral Cir Bucal* 2006; 11: E126–E129.
3. Aghahosseini F, *et al.* Methylene blue-mediated photodynamic therapy: a possible alternative treatment for oral lichen planus. *Lasers Surg Med* 2006; 38: 33–8.
4. Salah M, *et al.* Methylene blue mediated photodynamic therapy for resistant plaque psoriasis. *J Drugs Dermatol* 2009; 8: 42–9.
5. Fadel M, *et al.* Liposomal methylene blue hydrogel for selective photodynamic therapy of acne vulgaris. *J Drugs Dermatol* 2009; 8: 983–90.
6. Marotti J, *et al.* Photodynamic therapy can be effective as a treatment for herpes simplex labialis. *Photomed Laser Surg* 2009; 27: 357–63.
7. Tardivo JP, *et al.* New photodynamic therapy protocol to treat AIDS-related Kaposi's sarcoma. *Photomed Laser Surg* 2006; 24: 528–31.

Priapism. Priapism is usually treated with corporal aspiration or intracavernosal vasoconstrictors (see under Uses of Metaraminol, p. 1430.2). There have been reports[1-5] of the successful use of intracavernosal methylthioninium chloride, particularly in patients with drug-induced priapism; it is thought to act by blocking the vasodilator effects of nitric oxide. However, penile necrosis has occurred[6] after the use of methylthioninium chloride and it should probably be avoided in patients with corporal fibrosis; aspiration of methylthioninium chloride about 5 minutes after injection has been suggested.[2,3]

1. Steers WD, Selby JB. Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1991; 146: 1361–3.
2. deHoll JD, *et al.* Alternative approaches to the management of priapism. *Int J Impot Res* 1998; 10: 11–14.
3. Martínez Portillo FJ, *et al.* Methylene blue as a successful treatment alternative for pharmacologically induced priapism. *Eur Urol* 2001; 39: 20–3.
4. Hübler J, *et al.* Methylene blue as a means of treatment for priapism caused by intracavernous injection to combat erectile dysfunction. *Int Urol Nephrol* 2003; 35: 519–21.
5. Passavanti G, *et al.* From methylene blue (methylthionine chloride) to Al-Ghorab procedure: the therapy of priapism (our experience). *Arch Ital Urol Androl* 2009; 81: 242–4.
6. Mejean A, *et al.* Re: Use of methylene blue and selective embolization of the pudendal artery for high flow priapism refractory to medical and surgical treatments. *J Urol (Baltimore)* 1993; 149: 1149.

Adverse Effects and Precautions

After high intravenous doses, methylthioninium chloride may cause nausea, vomiting, abdominal and chest pain, headache, dizziness, mental confusion, profuse sweating, dyspnoea, and hypertension; methaemoglobinaemia and haemolysis may occur. Haemolytic anaemia and hyperbilirubinaemia have been reported in neonates after intra-amniotic injection.

Oral use may cause gastrointestinal disturbances and dysuria. Rash and a burning sensation have been reported with intravenous use and large doses are irritant to the urinary tract. Necrosis, abscesses, ulceration, and thrombophlebitis have also occurred after injection; subcutaneous use is not recommended. It should also not be given by intrathecal injection as neural damage has occurred. Intra-articular injection has resulted in effusion in the joint.

Anaphylactic reactions have occurred with methylthioninium. Other adverse effects include hypotension and arrhythmias.

The drug imparts a blue colour to saliva, urine, faeces, and skin, which may hinder a diagnosis of cyanosis. Use may result in an underestimation of the oxygen saturation reading in pulse oximetry. Methylthioninium chloride may also cause a false positive result in the phenolsulfonphthalein excretion test. Effects on the nervous system may impair the patient's ability to drive or operate machinery.

Methylthioninium chloride should be used with caution in patients with renal impairment and is not recommended in patients with G6PD deficiency (see below). Methylthioninium chloride is used to treat methaemoglobinaemia but in large doses it can itself produce methaemoglobinaemia and methaemoglobin concentration should therefore be closely monitored during treatment. Haemoglobin concentrations should also be monitored with long-term use as anaemia may occur. Methylthioninium chloride should not be used to treat methaemoglobinaemia induced by sodium nitrite during the treatment of cyanide poisoning, since cyanide binding will be reduced with resultant increased toxicity. Caution is required in methaemoglobinaemia due to chlorate poisoning as chlorate inactivates G6PD reducing the efficacy of treatment; there is also a risk of methylthioninium chloride catalysing chlorate to chlorite, increasing the production of methaemoglobin.

Aniline poisoning. It has been suggested[1] that methylthioninium chloride should be used with caution in the treatment of aniline-induced methaemoglobinaemia since it may precipitate Heinz body formation and haemolytic anaemia. Methylthioninium chloride may reduce methaemoglobin concentrations, but repeated doses could aggravate haemolysis without further reducing methaemoglobinaemia.

1. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. *Br J Haematol* 1983; 54: 29–41.

Effects on mental function. For reports of encephalopathy and CNS toxicity associated with the use of methylthioninium chloride see Interactions, p. 1561.1.

G6PD deficiency. Methylthioninium chloride is not effective for the treatment of methaemoglobinaemia in patients with G6PD deficiency as they have a diminished capacity to reduce methylthioninium chloride to leucomethylene blue (which in turn reduces methaemoglobin to haemoglobin); treatment is also potentially harmful as these patients are particularly susceptible to the haemolytic anaemias induced by methylthioninium chloride. Although most data support a risk of haemolytic anaemia, there have been reports of use in African men with G6PD deficiency without haemolysis.[1]

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.

Hypersensitivity. There are reports of anaphylactic reactions, including anaphylactic shock, with methylthioninium chloride.[1-4]

1. Rzymski P, *et al.* Anaphylactic reaction to methylene blue dye after laparoscopic chromopertubation. *Int J Gynaecol Obstet* 2003; 81: 71–2.
2. Dewachter P, *et al.* Severe anaphylactic shock with methylene blue instillation. *Anesth Analg* 2005; 101: 149–50.
3. Jangjoo A, *et al.* Anaphylaxis reaction of a breast cancer patient to methylene blue during breast surgery with sentinel node mapping. *Acta Oncol* 2010; 49: 877–8.
4. Nubret K, *et al.* Anaphylactic shock to fresh-frozen plasma inactivated with methylene blue. *Transfusion* 2011; 51: 125–8.

Necrosis. Necrosis has occurred in patients with breast cancer after methylthioninium chloride injection for sentinel lymph node biopsy, with skin and parenchymal necrosis after subdermal injection,[1] and skin and fat necrosis followed by dry gangrene after injection around the tumour.[2]

Penile necrosis has been reported after intracavernosal injection of methylthioninium chloride for priapism, see above.

1. Reyes FJ, *et al.* Complications of methylene blue dye in breast surgery: case reports and review of the literature. *J Cancer* 2011; 2: 20–5.
2. Salhab M, *et al.* Skin and fat necrosis of the breast following methylene blue dye injection for sentinel node biopsy in a patient with breast cancer. *Int Semin Surg Oncol* 2005; 2: 26.

Pregnancy. Although *intra-amniotic* injection of methylthioninium chloride has been used to diagnose premature rupture of fetal membranes or to identify separate amniotic sacs in twin pregnancies, there have been several reports of haemolytic anaemia (Heinz-body anaemia) and hyperbilirubinaemia in neonates who had been exposed to methylthioninium chloride in the amniotic cavity.[1-7] In most cases, exchange transfusions and/or phototherapy were required to control the jaundice; in 2 cases phototherapy led to a phototoxic reaction.[5,7] It has therefore been suggested[3,8] that the use of methylthioninium chloride for detecting premature rupture of the membranes should be avoided.

Multiple ileal occlusions have been reported in babies born to mothers who had twin pregnancies and who had received methylthioninium chloride by amniocentesis;[4,9,10] in some cases it was possible to determine that methylthioninium chloride had been injected into the amniotic sac of the affected twin. Analysis of data from the EUROCAT registries[11] for 1980 to 1988, which surveyed pregnancy outcomes in 11 countries, found a slightly higher risk of ileal and jejunal atresia or stenosis in twins regardless of whether they had received methylthioninium chloride, but the use of methylthioninium chloride was rare and no increased risk could be shown in babies exposed to it. Results from a retrospective cohort study[12] also suggested that there was a higher risk of fetal death after methylthioninium chloride for midtrimester amniocentesis in twin pregnancies. A review[8] from the CDC concluded that the epidemiological evidence for the teratogenicity of methylthioninium chloride was quite strong and advised that it should not be used for midtrimester amniocentesis.

A further difficulty in using methylthioninium chloride by amniocentesis for the diagnosis of premature rupture of the membranes is that the resultant staining of the skin and mucous membranes of the neonate hinders assessment of hypoxia, including the use of pulse oximetry.[13]

Although data on first trimester exposure to *intra-uterine* methylthioninium chloride are limited, there have been case reports with normal pregnancy outcomes.[14]

Oral methylthioninium chloride was not associated with an increased risk of malformations during the first trimester in 9 cases, or after the first trimester in 37 others.[15]

1. Cowett RM, *et al.* Untoward neonatal effect of intraamniotic administration of methylene blue. *Obstet Gynecol* 1976; 48 (suppl): 74s–75s.
2. Serota FT, *et al.* The methylene-blue baby. *Lancet* 1979; ii: 1142–3.
3. Crooks J. Haemolytic jaundice in a neonate after intra-amniotic injection of methylene blue. *Arch Dis Child* 1982; 57: 872–3.
4. Nicolini V, Monni G. Intestinal obstruction in babies exposed in utero to methylene blue. *Lancet* 1990; 336: 1258–9.
5. Porat R, *et al.* Methylene blue-induced phototoxicity: an unrecognized complication. *Pediatrics* 1996; 97: 717–21.
6. Gauthier TW. Methylene blue-induced hyperbilirubinemia in neonatal glucose-6-phosphate dehydrogenase (G6PD) deficiency. *J Matern Fetal Med* 2000; 9: 252–4.
7. George M. Methylene-blue-induced hyperbilirubinemia and phototoxicity in a neonate. *Clin Pediatr (Phila)* 2000; 39: 659–61.
8. Cragan JD. Teratogen update: methylene blue. *Teratology* 1999; 60: 42–8.
9. van der Pol JG, *et al.* Jejunal atresia related to the use of methylene blue in genetic amniocentesis in twins. *Br J Obstet Gynaecol* 1992; 99: 141–3.
10. Lancaster PAL, *et al.* Intra-amniotic methylene blue and intestinal atresia in twins. *J Perinat Med* 1992; 20 (suppl 1): 262.
11. Dolk H. Methylene blue and atresia or stenosis of ileum and jejunum. *Lancet* 1991; 338: 1021–2.
12. Kidd SA, *et al.* Fetal death after exposure to methylene blue dye during mid-trimester amniocentesis in twin pregnancy. *Prenat Diagn* 1996; 16: 39–47.
13. Troche BT. The methylene blue baby. *N Engl J Med* 1989; 320: 1756–7.
14. Gerli S, *et al.* Laparoscopy and methylene blue intrauterine injection immediately after undiagnosed conception: effect on pregnancy and neonatal outcome. *Eur J Obstet Gynecol Reprod Biol* 2004; 112: 102–3.
15. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Interactions

Serotonergic drugs. Methylthioninium chloride has been associated with reports of encephalopathy and CNS toxicity.[1-6] These generally occurred when given intravenously as a visualising agent for thyroid or parathyroid surgery or for the management of uncontrolled hypotension during cardiac surgery; all patients had recently received serotonergic drugs such as *bupropion, buspirone, clomipramine, mirtazapine, SSRIs,* or *venlafaxine,*[4,5] and symptoms were consistent with serotonin syndrome.[7] The MHRA in the UK therefore recommends that methylthioninium chloride should be avoided in patients recently treated with such drugs.

1. Khan MAS, *et al.* Prolonged postoperative altered mental status after methylene blue infusion during parathyroidectomy: a case report and review of the literature. *Ann R Coll Surg Engl* 2007; 89: W9–W11.
2. Sweet G, Standiford SB. Methylene-blue-associated encephalopathy. *J Am Coll Surg* 2007; 204: 454–8.
3. Ng BK, *et al.* Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review. *Can J Anaesth* 2008; 55: 36–41.
4. MHRA/CHM. Methylthioninium chloride (methylene blue): CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; 1 (6): 5–6. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON20335106&RevisionSelectionMethod=LatestReleased (accessed 19/07/08)
5. MHRA/CHM. Methylthioninium chloride (methylene blue): update on CNS toxicity with serotonergic drugs. *Drug Safety Update* 2008; 2 (9): 3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON0438106&RevisionSelectionMethod=LatestReleased (accessed 08/09/09)
6. Pollack G, *et al.* Parathyroid surgery and methylene blue: a review with guidelines for safe intraoperative use. *Laryngoscope* 2009; 119: 1941–6.
7. Ng BKW, Cameron AJD. The role of methylene blue in serotonin syndrome: a systematic review. *Psychosomatics* 2010; 51: 194–200.

Pharmacokinetics

Methylthioninium chloride is well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 to 2 hours after an oral dose. It is extensively distributed in the tissues where it is reduced to leucomethylene blue (leucomethylthioninium chloride). Most of a dose is excreted in the urine, mainly as leucomethylene blue with smaller amounts of unchanged drug; there is also excretion via the bile. It has a half-life of about 5 to 6.5 hours. Metabolism may be reduced in neonates (see Administration in Children, p. 1559.2).

References.

1. Peter C, *et al.* Pharmacokinetics and organ distribution of intravenous and oral methylene blue. *Eur J Clin Pharmacol* 2000; 56: 247–50.
2. Pruthi S, *et al.* Pharmacokinetics of methylene blue dye for lymphatic mapping in breast cancer—implications for use in pregnancy. *Am J Surg* 2011; 201: 70–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Metilenkek; *UK*: Provblue; *USA*: Urolene Blue†.

Multi-ingredient Preparations. *Arg.*: Mictasol Azul; Muelita; *Braz.*: Acridin; Cystex; Mictasol; Sepurin; Vislin; Visodin; *Canad.*: Blue Collyrium; Collyre Bleu Laiter; *Fr.*: Collyre Bleu; Pastilles Monleon†; *Hong Kong*: Clear Blue; *Israel*: Pronestin; *Ital.*: Visustrin; *Pol.*: Ginjal; Mibalin†; *Rus.*: Neo-Anusol (Неоанузол); *Spain*: Centilux; Ojosbel Azul†; *Switz.*: Collyre Bleu Laiter; *Turk.*: Buco Bleu; Helmo-Blue; Helmobleu; *USA*: Atrosept; Darpaz†; Hyophen; MHP-A; MSP-Blu; Phosphasal; Prosed/DS; UAA; Urelle; Uretron; Urimar-T; Urimax; Uriseptic; Uritact; Uro Blue; Urogesic Blue; Uryl; Ustell; Uticap; Utira; Utrona-C.

Pharmacopoeial Preparations
BP 2014: Methylthioninium Injection;
USP 36: Methylene Blue Injection.

Milk Thistle

Armurariul; Card burral; Card lleter; Card marià; Cardo Mariano; Chardon marie (milk-thistle fruit); Lady's Thistle; Maarianohdakkeenhedelmä (milk-thistle fruit); Margainių vaisiai (milk-thistle fruit); Mariadistel; Marian Thistle; Mariatistelfrukt (milk-thistle fruit); Mariendistel; Ostropest Plamisty; Ostropestřec Mariánský; Pegastl Badelj; Plod ostropestřece mariánského (milk-thistle fruit); Silybi mariani fructus (milk-thistle fruit); St Mary's Thistle; Tikrasis Margainis; Молочный Чертополох; Марьин Чертополох; Бял Трън.
CAS — 84604-20-6 (milk thistle extract).
ATC Herb — HA05BA5002 (Silybum marianum: fruit); HA05BA5003 (Silybum marianum: herb).
UNII — U946SH95EE (Silybum marianum seed); 822I9LEJ75 (Silybum marianum extract).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Milk-Thistle Fruit). The mature fruit, devoid of the pappus, of *Silybum marianum*. It contains not less than 1.5% of silymarin expressed as silibinin (dried drug).

USP 36: (Milk Thistle). The dried ripe fruit of *Silybum marianum* (Asteraceae), the pappus having been removed. It contains not less than 2% of silymarin, calculated as silibinin, on the dried basis. Store in airtight containers. Protect from light.

Silibinin *(rINN)*

Silibinina; Silibinine; Silibininum; Silybin; Silybum Substance E; Sylibina; Sylibinina; Szilibinin; Силибинин.
3,5,7-Trihydroxy-2-[3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxan-6-yl]-4-chromanone.
$C_{25}H_{22}O_{10}$=482.4
CAS — 22888-70-6.
UNII — 4RKY41TBTE.

NOTE. The name silymarin has been used for both a mixture of silibinin, silicristin, and silidianin, and for silibinin alone.

Silicristin *(rINN)*

Silicristina; Silicristine; Silicristinum; Silikrystyna; Silychristin; Силикристин.
2-[2,3-Dihydro-7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-5-benzofuranyl]-3,5,7-trihydroxy-4-chromanone.
$C_{25}H_{22}O_{10}$=482.4
CAS — 33889-69-9.
UNII — UK279ER14X.

Silidianin *(rINN)*

Silidianina; Silidianine; Silidianinum; Silydianin; Силидианин.
(+)-2,3α,3aα,7a-Tetrahydro-7aα-hydroxy-8(8')-(4-hydroxy-3-methoxyphenyl)-4-(3α,5,7-trihydroxy-4-oxo-2β-chromanyl)-3,6-methanobenzofuran-7(6a*H*)-one.
$C_{25}H_{22}O_{10}$=482.4
CAS — 29782-68-1.
UNII — 7P89L7W179.

Silymarin

Silimarina; Silymarinum.
A mixture of the isomers silibinin, silicristin, and silidianin.
CAS — 65666-07-1.
ATC — A05BA03.
ATC Vet — QA05BA03.

Profile

Milk thistle (*Silybum marianum; Carduus marianus*) is used in herbal medicine, mainly for gastrointestinal and hepatobiliary disorders. The fruit contains the active principle silymarin, a mixture of flavonolignans including the isomers silibinin, silicristin, and silidianin, of which silibinin is the major component. Silymarin is claimed to be a free radical scavenger and to have hepatoprotectant properties; it has been used in various liver disorders, as well as to prevent hepatotoxicity associated with poisoning. In *Amanita phalloides* mushroom poisoning (p. 2565.3) silibinin (as the disodium dihemisuccinate salt) is used.

Milk thistle is usually given as a standardised extract from the fruit containing mainly silymarin, although the herb has also been used; the strength of the extract is expressed in terms of silymarin or silibinin, although the exact equivalence is not always clear. It is usually given orally since silymarin is poorly water-soluble and therefore unsuitable for intravenous use. A typical oral dose of up to 140 mg of silymarin two or three times daily has been suggested for hepatic disorders. An oral dose of 108 mg silymarin up to twice daily has been given as a traditional remedy to relieve symptoms associated with overindulgence of food and drink, such as headache and upset stomach. Disodium silibinin dihemisuccinate is water-soluble and is given intravenously; 350 mg silibinin is equivalent to about 529 mg of the disodium dihemisuccinate. It is given, usually with beta-lactam antibacterials, in *Amanita phalloides* poisoning in a dose equivalent to silibinin 20 mg/kg daily, given in 4 divided doses, each by intravenous infusion over 2 hours.

References.

1. Saller R, *et al.* An updated systematic review with meta-analysis for the clinical evidence of silymarin. *Forsch Komplementmed* 2008; 15: 9–20.
2. Ramasamy K, Agarwal R. Multitargeted therapy of cancer by silymarin. *Cancer Lett* 2008; 269: 352–62.
3. Wu J-W, *et al.* Drug-drug interactions of silymarin on the perspective of pharmacokinetics. *J Ethnopharmacol* 2009; 121: 185–93.

Adverse effects. A report of acute generalised exanthematous pustulosis,[1] with extensive skin and oral lesions and raised serum creatinine, in a patient who had been drinking milk thistle tea for dyspepsia. Symptoms responded to treatment with oral prednisone. Subsequent skin tests confirmed hypersensitivity to an aqueous extract of milk thistle.

1. Ramírez-Santos A, *et al.* Pustulosis exantemática generalizada aguda debida a una infusión de cardo mariano (*Silybum marianum*). *Actas Dermosifiliogr* 2011. Available at: http://www.elsevier.es/sites/default/files/elsevier/eop/S0001-7310(11)00220-1.pdf (accessed 17/08/11)

Amanita poisoning. Silymarin and silibinin have been found to be effective in preventing hepatotoxicity after amanita poisoning.[1-3]

1. Lorenz D. Über die anwending von silibinin bei der knollenblätterpilzvergiftung. *Dtsch Arzt* 1982; 79: 43–5.
2. Hruby K, *et al.* Chemotherapy of Amanita phalloides poisoning with intravenous silibinin. *Hum Toxicol* 1983; 2: 183–90.
3. Enjalbert F, *et al.* Treatment of amatoxin poisoning: 20-year retrospective analysis. *J Toxicol Clin Toxicol* 2002; 40: 715–57.

Liver disorders. Milk thistle or silymarin has been used for various liver disorders including viral hepatitis, alcoholic liver disease, and cirrhosis.[1,2] Although some beneficial effects have been noted in individual studies, a systematic review considered most studies to be of poor quality and a significant effect on mortality or the complications of liver disease was not shown.[3]

1. Saller R, *et al.* The use of silymarin in the treatment of liver diseases. *Drugs* 2001; 61: 2035–63.
2. Abenavoli L, *et al.* Milk thistle in liver diseases: past, present, future. *Phytother Res* 2010; 24: 1423–32.
3. Rambaldi A, *et al.* Milk thistle for alcoholic and/or hepatitis B or C virus liver diseases. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 13/07/11).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Laragon; *Austral.*: Legalon; Liver-Vite†; *Austria*: Apihepar; Ardeyhepan; Legalon; *Belg.*: Legalon SIL; Legalon; *Braz.*: Forfig; Legalon; Siliver; *Chile*: Legalon; *China*: Legalon (利加隆); Shui Lin Jia (水林佳); *Cz.*: Flavobion; Lagosa; Legalon; Silygal†; *Fr.*: Legalon; *Ger.*: Alepa†; Alepafort; Ardeyhepan; Biocellflax†; Cefasilymarin; Hegrimarin†; Hepa-Loges; HepaBesch; Hepar-Pasc; Hepatos; Heplant; Lagosa; Legalon SIL; Legalon; Phytohepar; Silibene†; Silicur†; Silimarit; Silvaysan; *Gr.*: Legalon; *Hong Kong*: Legalon; *Hung.*: Hegrimarin; Legalon SIL; Legalon; Silegon; *India*: Alrin-B; Hepasil; Levalon; Limarin; Livosil; Marisil; Nitoliv; Silybon; *Indon.*: Liparin; *Ital.*: Legalon; Silimarin; Silirex; Silmar; Synchrorose; *Malaysia*: Cefasily; Legalon; *Mex.*: Etagerin†; Legalon; *Philipp.*: Hepavit; Heprotec; Legalon; Liver Plus; Liveraide; Livermate; *Pol.*: Flexiderm†; Lagosa; Legalon; Silimax; Sylicaps†; Sylimarol; Sylimarynal; Syliverin; *Port.*: Legalon SIL; Legalon; *Rus.*: Carsil (Карсил); Legalon (Леталон); Naturcarsevt (Натуркарсевт); Silimar (Силимар); *S.Afr.*: Legalon; *Singapore*: Legalon; *Spain*: Legalon SIL; Legalon; Silarine; *Switz.*: Legalon SIL; Legalon; *Thai.*: Legalon; Leveron; Liverin; Marina; Miltis; Pharmarin; Samarin; Sivylar†; *UK*: Digestive Relief; Indulgeze; Silamarie; Thisilyn; *Ukr.*: Carsil (Карсил); Darsil (Дарсил); Heparsil (Гепарсил)†; Legalon (Леталон); Legalon SIL (Леталон SIL); Silarsil (Силарсил); *Venez.*: Legalon.

Multi-ingredient Preparations. *Arg.*: Bibol Leloup; Quelodin F; *Austral.*: Antioxidant Forte Tablets†; Bio ACE Excell; Bupleurum Complex†; Bupleurum Compound; ChelaCo; Daily Plus Max†; Detox Program; DiGest; Extralife Liva-Care†; HerbaVital; Joint Ease; LivCo; Liver Detox; Liver Tonic Complex; Livton Complex; Mens Performance Multi; PM Syrin; St Mary's Thistle Plus†; Women's Vitality Multi; *Austria*: Hepabene†; Iberogast; *Braz.*: Silimalon; *Canad.*: Gallexier†; Milk Thistle Extract Formula; Milk Thistle†; Para-Gone; *Cz.*: Iberogast; Simepar; *Ger.*: Bilisan Duo†; Cholhepan N; Gallexier; Heumann Verdauungstee Solu-Lipar; Iberogast; *Hong Kong*: Hepatofalk Planta†; Simepar; *Hung.*: Hepabene; Iberogast; Majvedo es Detoxikalo; *India*: Alcohep; Alisia; Alrin-B; Arosi; Cancon; Denafed; Good Liver; Hepa; Hepasil-B; Hepawin Plus; Hosliv; Lecivit-S; Levalon; Livasa; Livasa; Livbel; Livbel; Liveril; Livopill; Livosil-B; Nitlor Plus; Palron; *Indon.*: Aptivium Liver Support†; Bio-Curliv; Curliv Plus; Curliv Plus; Cursil; Hepa-Q; Hepagard; Hepamax; Heparviton; Hepasil; Hepatin; Hepatofalk Planta†; Letrosil; Livercare; Naturliver; Proliva; Proliver; Verona; Vionin NF; *Ital.*: Berart; Depatox; Endoepatox; Legalon Plus; Legalon Plus; Linfoguard†; Liverton; *Malaysia*: Hepavite; Simepar; *Mon.*: Romarinex Chrome; *Neth.*: Iberogast; *Philipp.*: Hepamin; Hepavite; Liverine; Livermin; Liverpro; Liverton; *Pol.*: Artecholin†; Artecholwex†; Gastrobonisol; Iberogast; Sylicynar; Sylifex; Sylivit; Tabletki Przeciw Niestrawnosci; *Port.*: Synchrorose Intensivo; *Rus.*: Bonjigar (Бонджигар); Hepabene (Гепабене); Phosphonciale (Фосфонциале); Sibectan (Сибектан); *Singapore*: Hepasil DTX†; Hepatofalk Planta†; Hepavite; Simepar; *Spain*: Iberogast; *Swed.*: Iberogast; *Switz.*: Iberogast; Simepar; Tisane hepatique et biliaire; *UK*: Cypar; Digestisan; Milk Thistle Complex; *Ukr.*: Hepabene (Гепабене); Hepahealth (Гепахелс); Iberogast (Иберогаст); Levasil (Левасил); Livonorm (Ливонорм); Memory Booster (Мемори Бустер); PM Sirin (ПМ Сирин); Simepar (Симепар); *Venez.*: Hepasil.

Homoeopathic Preparations. *Austria*: Galstena; Gracil; Hamamelis-Homaccord; Lymphdiaral; Taraxacum Med Complex; Venodril; Vensa; *Canad.*: Carduus Plex†; Chelidonium Plex†; Cynara Complex†; Dandelion Combination†; Digestion; Formula FV 213; Hepar Compositum; Nixotinex; *Chile*: Calcarea fluor Compuesta; Formula II Especial; Variplant; *Cz.*: Hepeel; *Fr.*: Boripharm No 15†; Boripharm No 1†; Cheildonium Compose; Cholesterolum Complexe No 112†; Hepatodrainol; Homeodose

20†; L 114; L 28; Vascodran; Vascoflor; Yucca Complexe No 110; *Ger.*: Bomagall; Chelidonium comp; Chol-Do; Chola-Plantin N†; Chole-cyl L Ho-Len-Complex; Cholo 2-injektopas; Derivatio H; Derivatio; Galloselect; Gastro-Plantin N†; HanoHepan; Hepa-Gastreu N R7; Hepar comp; Hepar-Hevert N; Hepar-Hevert; Hepar-Hevert; Heparanox H; Infihepan; Lithias-cyl L Ho-Len-Complex; Marianon Hepar; Mariendistel Curarina; Ossidal; Phonix Silybum spag; phono Ven; Phyto-L; Rufebran heparo†; Spasmo-Bomaleb†; veno-loges N; Wibotin HM; *Hung.*: Hepeel; *Neth.*: Acidolite; Ailgeno spag; Dolilite; Hepa-Gastreu R7; Hepalite; Hepatodrainol†; Hepeel H; Lymphdiaral; *Port.*: Hepatodrainol; *Rus.*: Galstena (Галстена); Vensa (Венса); *Switz.*: Hepeel; metaheptachol; Regenaplex Nr. 35b; Regenaplex Nr. 80aN; *Ukr.*: Choledius (Холедиус); Galstena (Галстена); *USA*: Preferred Remedies Detoxin.

Pharmacopoeial Preparations
USP 36: Milk Thistle Capsules; Milk Thistle Tablets.

Nalmefene *(BAN, USAN, rINN)*

6-Desoxy-6-methylene-naltrexone; JF-1; Nalmefeeni; Nalmefen; Nalméfène; Nalmefeno; Nalmefenum; Nalmetrene; ORF-11676; Налмефен.

17-(Cyclopropylmethyl)-4,5α-epoxy-6-methylenemorphinan-3,14-diol.

$C_{21}H_{25}NO_3$=339.4

CAS — 55096-26-9.

UNII — TOV02TDP9I.

Nalmefene Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalmefeno; Nalméfène, Chlorhydrate de; Nalmefeni Hydrochloridum; Nalmefeno, hidrocloruro de; Nalmetrene Hydrochloride; Налмефена Гидрохлорид.

$C_{21}H_{25}NO_3$,HCl=375.9

CAS — 58895-64-0 (anhydrous nalmefene hydrochloride); 1228646-70-5 (nalmefene hydrochloride dihydrate).

UNII — K7K69QC05X (anhydrous nalmefene hydrochloride); 52Z0G7QVJX (nalmefene hydrochloride dihydrate).

Uses and Administration

Nalmefene is a derivative of naltrexone and is a specific opioid antagonist with actions similar to those of naloxone (p. 1563.1), but with a longer duration of action. It is given orally, as the hydrochloride dihydrate, as an adjunct in the management of alcohol dependence (p. 1734.1). Nalmefene is thought to act by modulating the activity of opioid receptors, which are involved in addiction, to reduce the urge to drink; it is used to help reduce the level of alcohol consumption in adult patients who have a high drinking risk, without physical withdrawal symptoms and who do not require immediate detoxification.

The patient's clinical status, alcohol dependence, and level of alcohol consumption should be evaluated before starting treatment with nalmefene; it should only be used in those who continue to have a high drinking risk level 2 weeks after the initial assessment. Nalmefene should be used on an as-required, rather than regular, basis; a single dose of 18 mg is taken preferably 1 to 2 hours before the anticipated time of drinking. If the patient has started drinking alcohol without taking nalmefene, a dose should be taken as soon as possible; no more than a single dose of 18 mg should be taken daily. Patients should be monitored regularly and the need for continued treatment evaluated on a regular basis; there are no clinical data for treatment longer than 1 year.

Anhydrous nalmefene hydrochloride has been given intravenously for the reversal of postoperative central depression due to the use of opioids and in the management of known or suspected opioid overdosage.

References.

1. Karhuvaara S, *et al.* Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 2007; 31: 1179–87.
2. Soyka M, Rösner S. Nalmefene for treatment of alcohol dependence. *Expert Opin Invest Drugs* 2010; 19: 1451–9.
3. Gual A, *et al.* BSENSE 2 Study Group. A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 2013; 23: 1432–42.
4. Keating GM. Nalmefene: a review of its use in the treatment of alcohol dependence. *CNS Drugs* 2013; 27: 761–72.

Gambling. For mention of the use of nalmefene in the treatment of gambling, see under Naltrexone, p. 1565.3.

Pruritus. It has been suggested that because central opioid receptors modulate itch, an opioid antagonist might be useful in pruritus (p. 1687.3).[1] A systematic review[2] found that opioid antagonists are effective in opioid-induced pruritus, and a number have also been reported to be of benefit in pruritus of other causes; some[1] recommend opioid antagonists as a treatment option for refractory cholestatic pruritus. Tachyphylaxis, loss of efficacy despite unchanged therapy, has been reported with long-term opioid antagonist treatment (from 1 to 9 months), and may be due to up-regulation of opioid receptors. An increase in dose or interruption in treatment for 2 to 3 weeks may restore the antipruritic effect.[1]

Rapid improvement of severe pruritus was reported after a single oral dose of *nalmefene* 10 or 20 mg in a double-blind study of 80 patients with either chronic urticaria or atopic dermatitis.[3] Pruritus was almost completely eliminated in up to 60% of patients receiving nalmefene. Adverse effects occurred in 67% of patients and included dizziness or lightheadedness, fatigue, and nausea. In another study,[4] 14 patients with resistant pruritus secondary to cholestatic liver disease were treated with oral nalmefene for 2 to 26 months. The initial dose was 2 mg twice daily and the dose was increased gradually as necessary. Although 13 of the patients reported some amelioration of pruritus, 5 found that increasing doses were required to produce any benefit, and in 3 tolerance appeared to develop.

Continuous infusion of *naloxone* 200 nanograms/kg per minute was reported to reduce perception of pruritus and scratching activity in a double-blind study of 29 patients with pruritus due to cholestasis,[5] although the role of continuous infusion in long-term management may be limited. A literature review[6] of opioid antagonists in the management of opioid-induced pruritus found most evidence supporting the use of continuous infusions of low-dose naloxone (range: 0.25 to 3 micrograms/kg per hour) for prevention in adults and children; however, doses above 2 micrograms/kg per hour are not generally recommended due to the risk of reversal of analgesia. Naloxone lotion is being investigated for the topical treatment of pruritus associated with cutaneous T-cell lymphoma such as mycosis fungoides.

Benefit has been reported with oral *naltrexone* 50 mg daily in pruritus of various origins,[7] as well as in patients with cholestatic pruritus.[8,9] In uraemic pruritus, conflicting results have been reported;[10,11] a subsequent study[12] suggested that naltrexone might be of benefit in selected patients.

1. Phan NQ, *et al.* Antipruritic treatment with systemic κ -opioid receptor antagonists: a review. *J Am Acad Dermatol* 2010; 63: 680–8.
2. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; 18: 346–57.
3. Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; 21: 135–6.
4. Bergasa NV, *et al.* Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; 27: 679–84.
5. Bergasa NV, *et al.* Effects of naloxone infusions in patients with the pruritus of cholestasis. *Ann Intern Med* 1995; 123: 161–7.
6. Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. *Am J Health-Syst Pharm* 2011; 68: 1419–25.
7. Metze D, *et al.* Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; 41: 533–9.
8. Wolfhagen FH, *et al.* Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; 113: 1264–9.
9. Terg R, *et al.* Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol* 2002; 37: 717–22.
10. Peer G, *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; 348: 1552–4.
11. Pauli-Magnus C, *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; 11: 514–9.
12. Legroux-Crespel E, *et al.* A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; 208: 326–30.

Adverse Effects and Precautions

For general adverse effects and precautions of opioid antagonists, see Naloxone, p. 1564.2 and p. 1564.3, respectively.

When used in the management of alcohol dependence, the most common adverse effects of nalmefene are nausea, dizziness, insomnia, and headache; most of these are mild or moderate and of short duration, and occur at the start of treatment. Confusional state and, rarely, hallucinations and dissociation have also been reported.

Therapeutic use of opioids should be avoided during nalmefene treatment. When analgesia is required, larger than usual doses of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects; close monitoring may be necessary. Nalmefene should be stopped 1 week before elective surgery involving opioid analgesia.

Nalmefene should be used with caution in patients with mild or moderate hepatic or renal impairment; it is contra-indicated in those with severe impairment.

Pharmacokinetics

Nalmefene is absorbed after oral doses but bioavailability is only about 40% owing to significant first-pass metabolism. Peak plasma concentrations occur about 1.5 hours after oral dosing; around 45% is bound to plasma proteins. It is metabolised in the liver, mainly to the inactive glucuronide, and is excreted in the urine. Some of the dose is excreted in the faeces and it may undergo enterohepatic recycling. The terminal elimination half-life after an intravenous or oral dose is reported to be about 10 or 12.5 hours, respectively.

References.

1. Dixon R, *et al.* Nalmefene: intravenous safety and kinetics of a new opioid antagonist. *Clin Pharmacol Ther* 1986; 39: 49–53.
2. Dixon R, *et al.* Nalmefene: safety and kinetics after single and multiple oral doses of a new opioid antagonist. *J Clin Pharmacol* 1987; 27: 233–9.
3. Frye RF, *et al.* The effect of age on the pharmacokinetics of the opioid antagonist nalmefene. *Br J Clin Pharmacol* 1996; 42: 301–6.
4. Frye RF, *et al.* Effects of liver disease on the disposition of the opioid antagonist nalmefene. *Clin Pharmacol Ther* 1997; 61: 15–23.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Lemeng (乐萌); Shuna (抒纳); *Mex.*: Nocarex†; *UK*: Selincro.

Nalorphine *(BAN, rINN)*

Nalorfiini; Nalorfin; Nalorfina; Nalorphin; Nalorphinum; Налорфин.

(-)-(5*R*,6*S*)-9a-Allyl-4,5-epoxymorphin-7-en-3,6-diol; 17-Allyl-17-normorphine.

$C_{19}H_{21}NO_3$=311.4

CAS — 62-67-9.

ATC — V03AB02.

ATC Vet — QV03AB02.

UNII — U59WB2WRY2.

Nalorphine Hydrobromide *(BANM, rINNM)*

Hidrobromuro de nalorfina; Nalorphine, Bromhydrate de; Nalorphini Hydrobromidum; Налорфина Гидробромид.

$C_{19}H_{21}NO_3$,HBr=392.3

CAS — 1041-90-3.

ATC — V03AB02.

ATC Vet — QV03AB02.

UNII — 1OLB66508A.

Pharmacopoeias. In *Chin.*

Nalorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalorfina; Nalorfina, hidrocloruro de; Nalorphine, Chlorhydrate de; Nalorphini Hydrochloridum; Nalorphinium Chloride; Налорфина Гидрохлорид.

$C_{19}H_{21}NO_3$,HCl=347.8

CAS — 57-29-4.

ATC — V03AB02.

ATC Vet — QV03AB02.

UNII — 9FPE56Z2TW.

Pharmacopoeias. In *US.*

USP 36: (Nalorphine Hydrochloride). Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Nalorphine is an opioid antagonist with properties similar to those of naloxone (p. 1563.1); in addition it also possesses some agonist properties and adverse effects such as drowsiness, respiratory depression, miosis, dysphoria, and lethargy may occur if it is given to patients who have not received opioids. It has been used as the hydrobromide or hydrochloride to reverse opioid-induced respiratory depression, but may exacerbate respiratory depression induced by alcohol or other non-opioid central depressants.

Preparations

Pharmacopoeial Preparations
USP 36: Nalorphine Hydrochloride Injection.

Naloxone Hydrochloride

(BANM, USAN, rINNM)

N-Allylnoroxymorphone Hydrochloride; Cloridrato de Naloxona; EN-15304; Hidrocloruro de naloxona; Nalokson Hidroklorür; Naloksonihydrokloridi; Naloksono hidrochloridas; Naloksonu chlorowodorek dwuwodny; Naloxona, hidrocloruro de; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydraté; Naloxon-hidroklorid; Naloxonhydrochlorid; Naloxonhydrochlorid; Naloxonhydrokloricl; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum; Налоксона Гидрохлорид.

17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (-)-(5*R*,14*S*)-9a-Allyl-4,5-

epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.
$C_{19}H_{21}NO_4,HCl,2H_2O=399.9$
CAS — 465-65-6 (naloxone); 357-08-4 (anhydrous naloxone hydrochloride); 51481-60-8 (naloxone hydrochloride dihydrate).
ATC — V03AB15.
ATC Vet — QV03AB15.
UNII — F850569PQR.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*. Forms specified may be anhydrous, dihydrate, or both.

Ph. Eur. 8: (Naloxone Hydrochloride Dihydrate; Naloxone Hydrochloride BP 2014). *It contains two molecules of water* of hydration. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.

USP 36: (Naloxone Hydrochloride). It is anhydrous or contains two molecules of water of hydration. A white to slightly off-white powder. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its aqueous solution is acidic. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Incompatibility. Infusions of naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or solutions with an alkaline pH.

Uses and Administration

Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is an antagonist of opioids that possess agonist or mixed agonist-antagonist activity although larger doses may be needed for compounds with the latter activity. It is used to reverse opioid central depression, including respiratory depression, induced by natural or synthetic opioids, in the management of known or suspected opioid overdosage, postoperatively after the use of opioids during surgery, and in neonates when opioid analgesics have been given to the mother during labour.

Naloxone hydrochloride is usually given intravenously for the most rapid action, with onset within 2 minutes. The onset of action is only slightly less rapid when it is given intramuscularly or subcutaneously. Other routes, including the endotracheal, have also been used. The duration of action of naloxone is dependent on the dose and route, but is generally in the range of 1 to 4 hours. An intravenous infusion may be used for a sustained response; commonly, 2 mg of naloxone hydrochloride is added to 500 mL of sodium chloride 0.9% or glucose 5% to obtain a concentration of 4 micrograms/mL.

In the management of known or suspected **opioid overdosage**, the initial dose of naloxone hydrochloride is 0.4 to 2 mg given intravenously and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used. When sustained opioid antagonism is needed, an intravenous infusion may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response. Some have recommended an infusion of 60% of the initial dose per hour given via an infusion pump, either undiluted, or diluted to a concentration of 200 micrograms/mL in glucose. Others have suggested an initial intravenous loading dose of 400 micrograms, followed by a continuous infusion at an initial rate of 400 micrograms/hour. Alternatively, an intravenous loading dose of 5 micrograms/kg has been suggested, followed by a continuous infusion of 2.5 micrograms/kg per hour.

Naloxone hydrochloride may also be used **postoperatively** to reverse central depression resulting from the use of opioids during surgery. A dose of 100 to 200 micrograms (corresponding to 1.5 to 3 micrograms/kg) may be given intravenously at intervals of 2 to 3 minutes, titrated for each patient in order to obtain an optimum respiratory response while maintaining adequate analgesia. If further doses are needed after 1 to 2 hours, they may be given by intramuscular injection or intravenous infusion for a sustained effect; infusions should be titrated according to response.

All patients receiving naloxone should be closely monitored as the duration of action of many opioids exceeds that of naloxone and repeated doses may be required.

For doses in children, see Administration in Children, below.

Naloxone hydrochloride is included in some oral opioid formulations to reduce the potential for parenteral abuse, or to counteract opioid-induced constipation. Naloxone hydrochloride has also been used cautiously in small doses to diagnose opioid dependence by precipitating the *withdrawal syndrome* (see p. 1564.2 and under Naltrexone, p. 1565.2).

Administration. Naloxone is usually given intravenously in opioid overdosage but may also be given intramuscularly or subcutaneously if intravenous access is not available. Alternative routes have also been tried; a study[1] using intranasal naloxone found that it was effective for prehospital management of suspected opioid overdosage, although response was slower than with intramuscular injection.

See also Administration in Children, below.

1. Kelly A-M, *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005; 182: 24–7.

Administration in children. In the **management of known or suspected opioid overdosage** in children, licensed product information recommends a usual initial dose of naloxone hydrochloride 10 micrograms/kg intravenously; if this does not result in the desired degree of clinical improvement, a subsequent dose of 100 micrograms/kg may be given. If the intravenous route is not feasible, naloxone can be given intramuscularly or subcutaneously in divided doses. The *BNFC* concurs with these doses for neonates and children up to the age of 12 years; those aged 12 years or older can be given the adult dose (see Uses and Administration, above). The *BNFC* also states that naloxone can be given by continuous intravenous infusion using an infusion pump, diluted to a concentration of 4 micrograms/mL in glucose 5% or sodium chloride 0.9%. Doses are recommended according to age:

- neonate to 12 years: 5 to 20 micrograms/kg per hour, adjusted according to response
- 12 to 18 years: 0.24 to 1.2 mg infused over 1 hour, then adjusted according to response

For **respiratory depression induced by opioid overdose**, the Committee on Drugs of the American Academy of Pediatrics[1] recommends initial naloxone doses as follows:

- neonates, and children under 5 years of age, or in those weighing less than 20 kg: 100 micrograms/kg
- children 5 years of age or older, or those weighing 20 kg or more: 2 mg

The American Heart Association[2] gives similar doses. Doses can be repeated as needed to maintain opiate reversal. Doses can be given by the intravenous,[1,2] intraosseous,[1,2] intramuscular, subcutaneous,[1] or endotracheal routes.[2] However, the American Academy of Pediatrics states that the endotracheal route is not recommended for neonates, and recommends intravenous or intramuscular use.[1] Intramuscular injection produces a more gradual and prolonged effect than intravenous administration but absorption may be erratic. The use of injections containing 20 micrograms/mL of naloxone hydrochloride is no longer recommended because of the fluid load involved at these doses, especially in small neonates.[3]

The American Academy of Pediatrics states that lower initial doses of 1 to 15 micrograms/kg may be considered for other clinical situations such as **respiratory depression associated with therapeutic opioid use.**[1] For complete or partial reversal of CNS depression caused by opioids, UK licensed product information for one preparation (*Hameln, UK*) suggests an initial intravenous dose of 10 to 20 micrograms/kg given at intervals of 2 to 3 minutes until satisfactory respiration and consciousness are obtained. Additional doses may be required at 1- to 2-hour intervals depending on the opioid and individual response. US licensed product information states that for **postoperative use**, initial doses of 5 to 10 micrograms may be given intravenously at 2- to 3-minute intervals until the desired response is obtained. In the UK, the *BNFC* suggests doses by intravenous injection according to age:

- neonate up to 12 years: 1 microgram/kg, repeated every 2 to 3 minutes if needed
- 12 to 18 years: 1.5 to 3 micrograms/kg, followed by a subsequent dose of 100 micrograms if needed

Opioid-induced depression in **neonates** resulting from the use of opioid analgesics in the mother during labour may be reversed by giving naloxone hydrochloride 10 micrograms/kg to the infant by intravenous, intramuscular, or subcutaneous injection, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single intramuscular dose of 60 micrograms/kg may be given at birth for a more prolonged action. Naloxone should be given with caution to the infants of opioid-dependent mothers since withdrawal symptoms can result.

1. Hegenbarth MA. American Academy of Pediatrics Committee on Drugs. Preparing for pediatric emergencies: drugs to consider. *Pediatrics* 2008; 121: 433–43. Also available at: http://pediatrics.aappublications.org/cgi/reprint/pediatrics;121/2/433.pdf (accessed 09/09/09)
2. Kleinman ME, *et al.* Part 14: pediatric advanced life support. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; 122 (suppl 3): S876–S908. Available at: http://circ.ahajournals.org/cgi/reprint/122/18_suppl_3/S876 (accessed 09/02/11)
3. American Academy of Pediatrics. Emergency drug doses for infants and children and naloxone use in newborns: clarification. *Pediatrics* 1989; 83: 803. Also available at: http://pediatrics.aappublications.org/cgi/reprint/83/5/803.pdf (accessed 17/08/10)

Administration in hepatic or renal impairment. Licensed product information for parenteral naloxone states that safety and efficacy have not been established in patients with hepatic or renal impairment, and caution is required. Naloxone plasma concentrations were reported to be about 6 times higher in patients with liver cirrhosis than those without liver disease.

A pharmacokinetic study[1] of an oral naltrexone plus opioid formulation in patients with severe hepatic impairment found that there were only minor differences in the bioavailability and elimination of total naloxone in those with hepatic impairment compared with healthy subjects. However, high concentrations of unconjugated naloxone were noted in those with hepatic impairment (in healthy subjects oral naloxone is inactivated during hepatic first-pass metabolism and unconjugated naloxone is usually undetectable), and the authors of the study theorised that systemically available naloxone might antagonise the analgesic effect of the opioid.

1. Brennscheidt U, *et al.* Pharmacokinetics of tilidine and naloxone in patients with severe hepatic impairment. *Arzneimittelforschung* 2007; 57: 106–11.

Administration with buprenorphine. Buprenorphine is a mixed opioid agonist/antagonist that dissociates slowly from opioid receptors (p. 31.1); naloxone may not completely reverse respiratory depression caused by buprenorphine. A pharmacokinetic study[1] found that a continuous intravenous infusion was the most effective way to give naloxone to prevent the recurrence of respiratory depression; a rate of 4 mg per 70 kg per hour was suggested.

Low-dose naloxone has been reported to increase the analgesic effect of buprenorphine.[2] This effect was dependent on the dose ratio of the 2 drugs, with a significant effect at a ratio of 15:1 buprenorphine to naloxone, but not at ratios above or below this. An increase in adverse effects was not seen. UK licensed product information also reports that naloxone may increase buprenorphine analgesia, and suggests that this may be the result of naloxone inhibiting the reduced analgesia sometimes seen with high doses of buprenorphine.

Naloxone is added to some sublingual formulations of buprenorphine used for opioid dependence to discourage parenteral abuse.

1. Yassen A, *et al.* Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. *Clin Pharmacokinet* 2007; 46: 965–80.
2. La Vincente SF, *et al.* Enhanced buprenorphine analgesia with the addition of ultra-low-dose naloxone in healthy subjects. *Clin Pharmacol Ther* 2008; 83: 144–52.

Eating disorders. Opioid antagonists including naloxone have been tried in the management of eating disorders, see Naltrexone, p. 1565.3.

Non-opioid overdosage. Naloxone antagonises the action of exogenous and endogenous opioids. This may explain the varying responses reported to naloxone used in the treatment of overdosage with non-opioids, some of which may modulate endogenous opioids.

Benefit has been reported[1] with naloxone in valproate overdosage, although the evidence is based on case reports. There have also been case reports suggesting benefit in overdosage with camylofin,[2] chlorpromazine,[3] and ibuprofen.[4] A study[5] with midazolam in healthy subjects found that naloxone did not reverse respiratory depression, although there had been earlier reports of benefit in coma due to benzodiazepines.

Naloxone has been used for clonidine intoxication, but retrospective reviews[6,7] have concluded that responses are inconsistent, and there have been reports of hypertension. The value of naloxone in brimonidine overdosage is also uncertain; although it has been used, a retrospective study in children found little evidence that it has any effect on outcomes.[8] There has been a report[9] of the successful use of naloxone after captopril overdosage.

Naloxone may also be of benefit in overdosage with drugs that are structurally related to opioids, including apomorphine,[10] dextromethorphan,[11] and loperamide.[12]

1. Roberge RJ, Francis EH. Use of naloxone in valproic acid overdose: case report and review. *J Emerg Med* 2002; 22: 67–70.
2. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; ii: 1246.
3. Chandavasu O, Chatkupt S. Central nervous system depression from chlorpromazine poisoning: successful treatment with naloxone. *J Pediatr* 1985; 106: 515–6.
4. Easley RB, Altemeier WA. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. *Pediatr Emerg Care* 2000; 16: 39–41.

5. Forster A, *et al.* Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. *Anesth Analg* 1983; 62: 920–4.
6. Piser DH, *et al.* Critical care for clonidine poisoning in toddlers. *Crit Care Med* 1990; 18: 1124–8.
7. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; 116: 654–8.
8. Lai Becker M, *et al.* Brimonidine tartrate poisoning in children: frequency, trends, and use of naloxone as an antidote. Abstract: *Pediatrics* 2009; 123: 590–1. Full version: http://pediatrics.aappublications.org/cgi/reprint/123/2/e305.pdf (accessed 11/09/09)
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; 20: 1125–7.
10. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; 14: 442–9.
11. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; 9: 237–8.
12. Friedli G, Baenggeli C-A. Loperamide overdose managed by naloxone. *Lancet* 1980; i: 1413.

Pruritus. For reference to the use of opioid antagonists, including naloxone, in the management of pruritus, see under Nalmefene, p. 1562.1

Reversal of opioid effects. Naloxone is used postoperatively to reverse central depression resulting from the use of opioids during surgery. However, the beneficial analgesic effects of the opioids may also be reversed, and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use.

In patients receiving longer-term opioids, low doses of naloxone have been reported to alleviate some of their adverse effects without loss of therapeutic efficacy, although results of studies have been inconsistent. Continuous intravenous infusion of naloxone reduced the incidence of adverse effects in patients receiving morphine by patient-controlled analgesia (PCA) for postoperative pain.[1] Pain control was not compromised and the lower dose of naloxone used (250 nanograms/kg hourly as opposed to 1 microgram/kg hourly) appeared to have an opioid-sparing effect. Adverse effects associated with intravenous tramadol were also reduced with a low-dose intravenous infusion of naloxone (50 to 200 nanograms/kg per hour) in one study[2]; analgesia was not affected. Additionally, naloxone reversed respiratory depression in a patient given intrathecal morphine,[3] without reversing analgesia. However, other studies have found neither improvement in morphine-induced adverse effects[4,5] nor any difference in analgesic requirements with use of intravenous naloxone, and a small study[6] in patients receiving extradural fentanyl found that naloxone failed to relieve urinary retention but pain scores rapidly increased. (A slightly larger study, however,[7] noted lower postoperative urinary residuals, more frequent voiding, fewer catheterisations, and comparable analgesia in patients who received intravenous naloxone with morphine PCA.)

Naloxone has been tried specifically to reduce pruritus associated with opioid therapy, again with variable effect. A subcutaneous dose of naloxone 400 micrograms did not prevent pruritus in women undergoing elective caesarean section;[8] however, when naloxone was added to a morphine and bupivacaine epidural post-hysterectomy, pruritus and nausea were reduced and analgesia maintained.[9]

Improvements in gastrointestinal adverse effects have been noted when naloxone was given with opioid analgesia. Intravenous naloxone has been shown to reverse the delay in gastric emptying induced by opioid analgesics in healthy subjects[10] and in women during labour.[11] Adding naloxone to a postoperative epidural was shown to reduce morphine-induced gut hypomotility without affecting analgesia,[12] and nausea and vomiting caused by epidural sufentanil were reduced when naloxone was included;[13] pain scores were also lower with naloxone. Naloxone has been given enterally to counteract constipation induced by opioid infusions in intensive care.[14] It has been reported to improve bowel function without compromising analgesia,[15] and is included in some oral prolonged-release opioid formulations. In patients receiving long-term oral opioids, oral naloxone in a daily dose equivalent to 20 to 40% of the daily opioid dose relieved opioid-induced constipation without compromising analgesic control.[16,17] Doses equivalent to 10% or less of the opioid dose were ineffective.[18] However, other studies[19] have found adverse effects even at low doses of naloxone, and the optimum dose remains unclear.

It has been suggested that naloxone may limit opioid tolerance; however, an intravenous infusion of naloxone 250 nanograms/kg per hour did not reduce fentanyl requirements in critically-ill children.[20]

Methylnaltrexone, a related opioid antagonist is used for the reversal of opioid-induced constipation (see p. 1861.3).

1. Gan TJ, *et al.* Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997; 87: 1075–81.
2. Jia D-L, *et al.* A small-dose naloxone infusion alleviates nausea and sedation without impacting analgesia via intravenous tramadol. *Chin Med J (Engl)* 2010; 123: 1695–8.
3. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. *BMJ* 1980; 281: 645–6.
4. Sartain JB, *et al.* Effect of combining naloxone and morphine for intravenous patient-controlled analgesia. *Anesthesiology* 2003; 99: 148–51.
5. Greenwald PW, *et al.* Low-dose naloxone does not improve morphine-induced nausea, vomiting, or pruritus. *Am J Emerg Med* 2005; 23: 35–9.
6. Wang J, *et al.* Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. *Br J Anaesth* 1998; 80: 565–6.
7. Gallo S, *et al.* A study of naloxone effect on urinary retention in the patient receiving morphine patient-controlled analgesia. *Orthop Nurs* 2008; 27: 111–15.
8. Lockington PF, Fa'aea P. Subcutaneous naloxone for the prevention of intrathecal morphine induced pruritus in elective Caesarean delivery. *Anaesthesia* 2007; 62: 672–6.
9. Choi JH, *et al.* Epidural naloxone reduces pruritus and nausea without affecting analgesia by epidural morphine in bupivacaine. *Can J Anaesth* 2000; 47: 33–7.
10. Nimmo WS, *et al.* Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *BMJ* 1979; 2: 1189.
11. Frame WT, *et al.* Effect of naloxone on gastric emptying during labour. *Br J Anaesth* 1984; 56: 263–5.
12. Lee J, *et al.* Epidural naloxone reduces intestinal hypomotility but not analgesia of epidural morphine. *Can J Anaesth* 2001; 48: 54–8.
13. Kim MK, *et al.* Epidural naloxone reduces postoperative nausea and vomiting in patients receiving epidural sufentanil for postoperative analgesia. *Br J Anaesth* 2007; 99: 270–5.
14. Arpino PA, Thompson BT. Safety of enteral naloxone for the reversal of opiate-induced constipation in the intensive care unit. *J Clin Pharm Ther* 2009; 34: 171–5.
15. Löwenstein O, *et al.* Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol* 2010; 10: 12.
16. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; 337: 1475.
17. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; 338: 582.
18. Robinson BA, *et al.* Oral naloxone in opioid-associated constipation. *Lancet* 1991; 338: 581–2.
19. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. *Am J Health-Syst Pharm* 2003; 60: 1264–7.
20. Darnell CM, *et al.* Effect of low-dose naloxone infusion on fentanyl requirements in critically ill children. *Pediatrics* 2008; 121: e1363–e1371. Also available at: http://pediatrics.aappublications.org/cgi/reprint/121/5/e1363 (accessed 14/02/11)

DIAGNOSTIC USE. Naloxone is used to reverse opioid effects in the diagnosis of opioid overdose, although some workers have recommended that it should only be used in patients with clinical signs of opioid overdose.[1]

Naloxone has also been used in the diagnosis of opioid dependence. It has been given intravenously to precipitate withdrawal symptoms, but methods that do not induce acute withdrawal have also been investigated. Pupillary dilatation in response to topical naloxone solution (naloxone eye drops) has been suggested as a useful method, but varying results have been reported depending on the strength of the solution used. A study[2] using naloxone hydrochloride solution 1 mg/mL distinguished patients with a physical dependence from non-dependent patients who had received opioids on a single occasion as pre-operative medication, but this response was not confirmed in another study[3] using naloxone 400 micrograms/mL solution. Another study[4] reported that a 2 mg/mL solution of naloxone hydrochloride gave useful results in an outpatient setting. However, there has been a report[5] of withdrawal syndrome and pupillary dilatation in 4 opioid dependent subjects after instillation of naloxone solution 40 mg/mL.

1. Hoffman JR, *et al.* The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991; 20: 246–52.
2. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; i: 748–50.
3. Lotmer N, *et al.* Conjunctival naloxone is no decision aid in opioid addiction. *Lancet* 1990; 335: 1107–8.
4. Ghodse AH, *et al.* Evaluation of the opioid addiction test in an out-patient drug dependency unit. *Br J Psychiatry* 1999; 175: 158–62.
5. Sanchez-Ramos JR, Senay EC. Ophthalmic naloxone elicits abstinence in opioid-dependent subjects. *Br J Addict* 1987; 82: 313–15.

Shock. Endogenous opioids may have a role in the pathophysiology of shock but studies investigating naloxone for the treatment of shock have produced contradictory results. A systematic review[1] concluded that naloxone does increase blood pressure in various forms of shock, but no significant effect on mortality was shown. US licensed product information has noted that the optimal dose and duration of therapy with naloxone have not been established, and that caution should be exercised before its use, particularly in patients with underlying pain or who have previously received opioids and may have developed opioid tolerance.

1. Boeuf B, *et al.* Naloxone for shock. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 04/10/05).

Adverse Effects

Opioid antagonists are generally considered to have little, if any, intrinsic action. When they are given in the absence of opioids, or to reverse the effects of opioids in non-opioid dependent patients, adverse effects are generally mild.

Adverse effects associated with competitive opioid antagonists may be caused by the reversal of opioid effects such as opioid withdrawal symptoms (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). Other reported effects on the nervous system include dizziness, headache, hallucinations, and excitement; seizures have occurred rarely. Effects on the cardiovascular system include hypertension or hypotension, tachycardia or bradycardia, ventricular fibrillation, myocardial infarction, and heart failure. Opioid antagonists may stimulate the release of some hormones such as those from the pituitary. Hypersensitivity reactions such as anaphylactic shock, urticaria, dyspnoea, and angioedema have been reported with parenteral use.

Other adverse effects reported with naloxone include arrhythmias, pulmonary oedema, coma, and encephalopathy, usually with postoperative use; fatalities have occurred. There are rare reports of erythema multiforme. Large doses of naloxone and rapid reversal of opioid effects may contribute to the development of adverse effects.

Effects on the cardiovascular system. Hypertension,[1,2] pulmonary oedema,[3] and cardiac arrhythmias including ventricular tachycardia and fibrillation[4] have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients,[5,6] including some fatalities.[5]

Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke.[7]

Ventricular fibrillation has been seen in an opioid addict given naloxone to reverse the effects of diamorphine.[8] However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the UK *National Poisons Information Service* noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year.[9] In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication.[10] The effects were: asystole (1 case), generalised convulsions (3 cases), pulmonary oedema (1 case), and violent behaviour (1 case).

1. Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; 228: 25–6.
2. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; 58: 524–5.
3. Flacke JW, *et al.* Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; 47: 376–8.
4. Michaelis LL, *et al.* Ventricular irritability associated with the use of naloxone hydrochloride: two case reports and laboratory assessment of the effects of the drug on cardiac excitability. *Ann Thorac Surg* 1974; 18: 608–14.
5. Wride SRN, *et al.* A fatal case of pulmonary oedema in a healthy young male following naloxone administration. *Anaesth Intensive Care* 1989; 17: 374–7.
6. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; 59: 576–7.
7. Barsan WG, *et al.* Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; 17: 762–7.
8. Cuss FM, *et al.* Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; 288: 363–4.
9. Barret L, *et al.* Cardiac arrest following naloxone. *BMJ* 1984; 288: 936.
10. Osterwalder JJ. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; 34: 409–16.

Precautions

Naloxone should be used with caution in patients physically dependent on opioids, or who have received large doses of opioids, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). A withdrawal syndrome may be precipitated in neonates of opioid-dependent mothers when naloxone is used in the neonate, or when it is given during pregnancy, as it crosses the placenta. Analgesia may be reversed when naloxone is used postoperatively.

Caution is required in patients with cardiac disease or those receiving cardiotoxic drugs.

The duration of action of some opioids exceeds that of naloxone; patients should therefore be carefully monitored after use in case of relapse. Reversal of respiratory depression due to partial opioid agonists or mixed agonists/antagonists such as buprenorphine may be incomplete, see also Administration with Buprenorphine, p. 1563.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naloxone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pharmacokinetics

Naloxone is absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism. It is extensively distributed into body tissues and fluids, particularly the brain as it is highly lipophilic. Protein binding is about 32 to 45%. It is metabolised in the liver,

mainly by glucuronide conjugation, with naloxone-3-glucuronide as the major metabolite. It is excreted in the urine as metabolites. It has a plasma half-life of about 1 to 1.5 hours after parenteral doses in adults, and around 3 hours in neonates. Naloxone crosses the placenta.

Pregnancy and the neonate. A study in 30 mothers given a single intravenous dose of naloxone during the second stage of labour, indicated that naloxone rapidly crossed the placental barrier so that some therapeutic effect might be anticipated in most neonates.[1] Placental transfer in 7 further mothers given naloxone intramuscularly was considered to be too variable for therapeutic purposes.

In 12 neonates given naloxone hydrochloride 35 or 70 micrograms intravenously via the umbilical vein, the mean plasma half-life was 3.53 or 2.65 hours respectively.[2] These half-lives were 2 to 3 times longer than those reported for adults, possibly due to a diminished ability of the newborn to metabolise drugs by conjugation with glucuronic acid. Mean peak plasma concentrations of 8.2 nanograms/mL or 13.7 nanograms/mL in those given 35 or 70 micrograms respectively, were reached within 40 minutes but this time was very variable, and in 5 neonates peak concentrations were reached within 5 minutes. Naloxone hydrochloride 200 micrograms intramuscularly in 17 further neonates produced peak concentrations of 7.4 to 34.6 nanograms/mL at 0.5 to 2 hours.

1. Hibbard BM, *et al.* Placental transfer of naloxone. *Br J Anaesth* 1986; 58: 45–8.
2. Moreland TA, *et al.* Naloxone pharmacokinetics in the newborn. *Br J Clin Pharmacol* 1980; 9: 609–12.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antiopiaz†; Grayxona; Narcantil†; Narxona; *Austral.*: Narcan†; *Braz.*: Narcan; *China*: Feng Du (风度); Fu Er Xin (富尔欣); Jian Tian Neng (健天能); Jin Er Lun (金尔伦); Kawin Nuotong (凯因诺彤); Na Le Shu (纳乐枢); Rui Luo Jian (瑞络健); Sai Xian (赛先); Su Nuo (苏诺); Xin Pu Ao (欣浦澳); Xinqing (欣晴); *Cz.*: Intrenon; Nexodal; *Denm.*: Nexodal; *Fin.*: Nexodal; *Fr.*: Nalone†; Narcan; *Gr.*: Narcan; *Hong Kong*: Mapin†; *India*: Nalox; Narcotan; Nex; *Indon.*: Nokoba; *Irl.*: Narcan†; Nexodal†; *Ital.*: Narcan; *Malaysia*: Mapin; *Neth.*: Nexodal†; *Norw.*: Nexodal; *NZ*: Narcan; *Philipp.*: Narcotan; Narlox; *Port.*: Naxan; Naxolan; Nexodal; *Rus.*: Naloxon (Налоксон); *S.Afr.*: Narcan; Zynox†; *Singapore*: Mapin; Narcan; *Swed.*: Nexodal; *Thai.*: Narcan; *UK*: Prenoxad; *Venez.*: Narcan; Oxogina.

Multi-ingredient Preparations. *USA*: Zubsolv.

Used as an adjunct in:. *Austral.*: Suboxone; Targin; *Austria*: Suboxone; Targin; *Belg.*: Suboxone; Targinact; Tinalox; Valtran; *Canad.*: Suboxone; Targin; *Cz.*: Suboxone; Targin; *Denm.*: Suboxone; Targin; *Fin.*: Targiniq; *Fr.*: Suboxone; Targinact; *Ger.*: Andolor†; Celldolor†; Nalidin†; Suboxone; Targin; Tili Compt†; Tili-Puren†; Tilicomp; Tilidin compt†; Tilidin N†; Tilidin plus; Tilidin-saar†; Tilidin; Tilnalox†; Valoron N; *Gr.*: Suboxone; *Hong Kong*: Suboxone; *Hung.*: Suboxone; *Indon.*: Suboxone; *Irl.*: Suboxone; Targin; *Israel*: Targin; *Ital.*: Suboxone; Targin; *Jpn*: Peltazon; Pentagin; Sosegon; *Malaysia*: Suboxone; *Neth.*: Suboxone; Targinact; *Norw.*: Suboxone; Targiniq; *NZ*: Suboxone; Targin; *Pol.*: Suboxone; *Port.*: Suboxone; *Singapore*: Targin; *Spain*: Suboxone; Targin; *Swed.*: Suboxone; Targiniq; *Switz.*: Targin; *Turk.*: Suboxone; *UK*: Suboxone; Targinact; *USA*: Suboxone; Talwin NX†.

Pharmacopoeial Preparations

BP 2014: Naloxone Injection; Neonatal Naloxone Injection;
USP 36: Naloxone Hydrochloride Injection; Pentazocine and Naloxone Tablets.

Naltrexone *(BAN, USAN, rINN)*

Naltrekson; Naltreksoni; Naltrexon; Naltrexona; Naltrexonum; Налтрексон.

(5*R*)-9a-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one; 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

$C_{20}H_{23}NO_4$=341.4

CAS — 16590-41-3.

ATC — N07BB04.

ATC Vet — QN07BB04; QV03AB30.

UNII — 5S6W795CQM.

Naltrexone Hydrochloride *(BANM, rINNM)*

EN-1639A; Hidrocloruro de naltrexona; Naltreksonihydroklorid; Naltreksono hidrochloridas; Naltrexona, hidrocloruro de; Naltrexone, Chlorhydrate de; Naltrexonhydrochlorid; Naltrexon-hydroklorid; Naltrexonhydroklorid; Naltrexoni hydrochloridum; Налтрексона Гидрохлорид.

$C_{20}H_{23}NO_4$,HCl=377.9

CAS — 16676-29-2.

ATC — N07BB04.

ATC Vet — QN07BB04.

UNII — Z6375YW95F.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Naltrexone Hydrochloride). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Naltrexone Hydrochloride). Store in airtight containers.

Uses and Administration

Naltrexone is a specific opioid antagonist with actions similar to those of naloxone (p. 1563.1); however, it is more potent than naloxone and has a longer duration of action. It is used in the management of opioid dependence and alcohol dependence.

Naltrexone hydrochloride is used as an aid to maintaining abstinence after opioid withdrawal in detoxified, formerly **opioid-dependent** patients. Naltrexone treatment should not be started until the patient has been detoxified and abstinent from opioids for at least 7 to 10 days because of the risk of acute withdrawal; abstinence should be verified by analysis of the patient's urine. A *naloxone challenge test* may then be used to confirm the absence of opioids, as follows: naloxone hydrochloride 200 micrograms is given intravenously and the patient monitored for 30 seconds for evidence of withdrawal symptoms; if none occur, a further dose of 600 micrograms is given and the patient monitored for 20 to 30 minutes. A confirmatory rechallenge with naloxone hydrochloride 1.6 mg intravenously may be considered if results are ambiguous. US licensed product information suggests a naloxone challenge test with a single dose of 800 micrograms given subcutaneously as an alternative to the intravenous route.

Once a negative naloxone challenge test has been obtained, naltrexone hydrochloride is given to maintain abstinence. An oral dose of 25 mg may be given initially. If no signs of opioid withdrawal occur subsequent doses may be increased to 50 mg daily. The usual maintenance dose of naltrexone hydrochloride is 350 mg weekly given as 50 mg daily, but the dosing interval may be lengthened to improve compliance; for example, doses of 100 mg on Monday and Wednesday and 150 mg on Friday may be effective, and various other intermittent dosage regimens have been used. Alternatively, naltrexone (as the base) may be given as a long-acting modified-release intramuscular injection in a dose of 380 mg once every 4 weeks. Patients should be carefully counselled and warned that attempts to overcome the opioid blockade with large doses of opioids could result in fatal opioid intoxication.

Naltrexone hydrochloride is also used as an adjunct in the management of **alcohol dependence** at a recommended oral dose of 50 mg daily. Alternatively, naltrexone (as the base) may be given as a modified-release intramuscular injection in a dose of 380 mg once every 4 weeks.

Naltrexone hydrochloride is included in some oral opioid formulations to reduce the potential for parenteral abuse.

Alcohol withdrawal and abstinence. Naltrexone may be of use as an adjunct to psychotherapy in maintaining abstinence after alcohol withdrawal in patients with alcohol dependence (p. 1734.1).[1,2] Two systematic reviews have concluded that oral naltrexone is safe and effective for treatment of alcohol dependence,[2,3] although there is less evidence for long-term benefit.[3] However, since the risk of relapse is particularly high early after alcohol withdrawal, treatment for at least 6 months has been recommended.[4] Compliance with oral naltrexone may be a problem,[2,3] and promising results[2,5–7] have been reported with a long-acting intramuscular injection given monthly.

Although it has been suggested that there may be a difference in response to naltrexone treatment for alcohol dependency depending on gender, results from studies have been conflicting. Some have reported little effect on drinking in women treated with naltrexone and cognitive behaviour therapy,[8] while others have reported either a greater effect in women than men,[9] or less effect in women than men (in those with alcohol plus cocaine dependence).[10] In contrast, women and men had a similar response to naltrexone in an analysis of data from a larger study,[11] and naltrexone was suggested as a viable treatment option for both sexes.

Naltrexone appears to be more effective at reducing the amount of alcohol consumed than producing complete abstinence;[3] reports[12] from patients who continued to drink during therapy suggest that naltrexone may reduce the pleasure associated with drinking, possibly by blocking the effect of endorphins released as a result of alcohol consumption.

Although naltrexone does not appear to be hepatotoxic at the oral dosage of 50 mg daily used for alcohol dependence, caution is recommended in patients with liver disease;[4] careful monitoring is recommended if it is given with disulfiram since hepatotoxicity could potentially be increased.

Nalmefene, a derivative of naltrexone, is also used as an adjunct in the management of alcohol dependence (for details see under Nalmefene, p. 1562.1).

1. Anton RF. Naltrexone for the management of alcohol dependence. *N Engl J Med* 2008; 359: 715–21.
2. Rösner S, *et al.* Opioid antagonists for alcohol dependence. Available in The Cochrane Database of Systematic Reviews; Issue 12. Chichester: John Wiley; 2010 (accessed 10/02/11).
3. Bouza C, *et al.* Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: a systematic review. *Addiction* 2004; 99: 811–28.
4. Berg BJ, *et al.* A risk-benefit assessment of naltrexone in the treatment of alcohol dependence. *Drug Safety* 1996; 15: 274–82.
5. Garbutt JC, *et al.* Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA* 2005; 293: 1617–25. Correction. *ibid.*: 1978.
6. Swainston Harrison T, *et al.* Extended-release intramuscular naltrexone. *Drugs* 2006; 66: 1741–51.
7. Ciraulo DA, *et al.* Early treatment response in alcohol dependence with extended-release naltrexone. *J Clin Psychiatry* 2008; 69: 190–5.
8. O'Malley SS, *et al.* Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. *Alcohol Clin Exp Res* 2007; 31: 625–34.
9. Kiefer F, *et al.* A neuroendocrinological hypothesis on gender effects of naltrexone in relapse prevention treatment. *Pharmacopsychiatry* 2005; 38: 184–6.
10. Pettinati HM, *et al.* Gender differences with high-dose naltrexone in cocaine and alcohol dependence. *J Subst Abuse Treat* 2008; 34: 378–90.
11. Greenfield SF, *et al.* Gender differences in alcohol treatment: an analysis of outcome from the COMBINE study. *Alcohol Clin Exp Res* 2010; 34: 1803–12.
12. Volpicelli JR, *et al.* Effect of naltrexone on alcohol "high" in alcoholics. *Am J Psychiatry* 1995; 152: 613–15.

Autism. Autistic disorders have been linked with abnormalities in the endogenous opioid system and there is some evidence[1] that naltrexone may be of benefit in children with autism, especially in those with self-injurious behaviour.

1. ElChaar GM, *et al.* Efficacy and safety of naltrexone use in pediatric patients with autistic disorder. *Ann Pharmacother* 2006; 40: 1086–95.

Eating disorders. Endogenous opioids may have a role in the pathophysiology of eating disorders,[1] thus opioid antagonists such as naloxone and naltrexone have been tried in their management. Naltrexone is under investigation, combined with bupropion, in the management of obesity.[2–7] In one study[6] mean weight loss in participants taking oral naltrexone 32 mg plus bupropion for up to 56 weeks was 6.1 kg compared with 1.4 kg in those taking placebo.

Naltrexone has also been tried in anorexia and other eating disorders.[8,9]

1. de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. *J Clin Pharmacol* 1992; 32: 1060–72.
2. Lee MW, Pujioka K. Naltrexone for the treatment of obesity: review and update. *Expert Opin Pharmacother* 2009; 10: 1841–5.
3. Greenway FL, *et al.* NB-201 Study Group. Comparison of combined bupropion and naltrexone therapy for obesity with monotherapy and placebo. *J Clin Endocrinol Metab* 2009; 94: 4898–4906.
4. Plodkowski RA, *et al.* Bupropion and naltrexone: a review of their use individually and in combination for the treatment of obesity. *Expert Opin Pharmacother* 2009; 10: 1069–81.
5. Padwal R. Contrave, a bupropion and naltrexone combination therapy for the potential treatment of obesity. *Curr Opin Investig Drugs* 2009; 10: 1117–25.
6. Greenway FL, *et al.* COR-I Study Group. Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2010; 376: 595–605. Corrections, *ibid.*: 594 and 1392.
7. Wadden TA, *et al.* Weight loss with naltrexone SR/bupropion SR combination therapy as an adjunct to behavior modification: the COR-BMOD trial. *Obesity (Silver Spring)* 2011; 19: 110–20.
8. Gade K, *et al.* Atypical anorexia in a male patient accompanied by strong obsessive-compulsive symptoms successfully treated with naltrexone. *Pharmacopsychiatry* 2009; 42: 164–5.
9. Kmoch V, *et al.* Two patients with eating disorders treated by naltrexone. *Neuro Endocrinol Lett* 2009; 30: 327–30.

Gambling. Naltrexone has been tried for pathological gambling with some success.[1] Nalmefene has also been investigated, but with variable results.[2,3]

1. Grant JE, *et al.* A double-blind, placebo-controlled study of the opiate antagonist naltrexone in the treatment of pathological gambling urges. *J Clin Psychiatry* 2008; 69: 783–9.
2. Grant JE, *et al.* Multicenter investigation of the opioid antagonist nalmefene in the treatment of pathological gambling. *Am J Psychiatry* 2006; 163: 303–12.
3. Grant JE, *et al.* Nalmefene in the treatment of pathological gambling: multicentre, double-blind, placebo-controlled study. *Br J Psychiatry* 2010; 197: 330–1.

Opioid dependence. *MAINTENANCE.* Naltrexone is a long-acting, non-addictive oral opioid antagonist. It is considered effective in maintaining abstinence in opioid addicts after detoxification, although a systematic review[1] noted that evidence of superiority to other treatments (including placebo) was lacking, and compliance with therapy is difficult to maintain because although naltrexone blocks the euphoriant effects of opioids it does not block the craving

for them. It is thus most effective in highly motivated addicts with good sociological and psychological support to discourage impulsive use of opioids.[1-4] Modified-release injectable naltrexone may be used for maintenance, and may increase adherence to treatment,[5] although evidence of efficacy is limited.[6] Complications have been reported with depot injections, including opioid withdrawal[7] and ineffective analgesia after surgery.[7] There is a risk of overdose if opioids are used to overcome the antagonist effect of naltrexone; although there are rare reports of deaths after opioid and non-opioid overdoses in patients with naltrexone implants,[8] it is not clear if the risk is different than might be expected in such patients.[9,10] Precautions relating to naloxone use should be noted, see below.

For a discussion of the management of opioid dependence, see p. 109.2.

1. Minozzi S, *et al.* Oral naltrexone maintenance treatment for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 03/03/11).
2. George S, Ekhtiari H. Naltrexone in the treatment of opioid dependence. *Br J Hosp Med* 2010; 71: 568–70.
3. NICE. Naltrexone for the management of opioid dependence: Technology Appraisal Guidance 115 (issued January 2007). Available at: http://guidance.nice.org.uk/TA115/guidance/pdf/English (accessed 02/05/07)
4. Adi Y, *et al.* Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation. *Health Technol Assess* 2007; 11: iii–iv, 1–85. Also available at: http://www.hta.ac.uk/fullmono/mon1106.pdf (accessed 15/02/11)
5. Comer SD, *et al.* Injectable, sustained-release naltrexone for the treatment of opioid dependence: a randomized, placebo-controlled trial. *Arch Gen Psychiatry* 2006; 63: 210–18.
6. Lobmaier P, *et al.* Sustained-release naltrexone for opioid dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 21/07/08).
7. Linzeris N, *et al.* Unplanned admissions to two Sydney public hospitals after naltrexone implants. *Med J Aust* 2008; 188: 441–4.
8. Gibson AE, *et al.* Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 186: 152–3.
9. Hulse GK, Tait RJ. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 187: 54.
10. Sim MG-B. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust* 2007; 187: 54.

RAPID DETOXIFICATION. Naltrexone has been used in various regimens for rapid detoxification;[1,2] opioid withdrawal may be achieved in only a few days, although benefits for long-term outcome are not yet established. It has also been used for ultrarapid detoxification under anaesthesia, although a systematic review[3] concluded that the risks outweighed the benefits of using opioid antagonists in such procedures. A later study[4] also failed to support the use of such a regimen.

Use of a subcutaneous implant of naltrexone for rapid opioid detoxification has been associated with complications, including pulmonary oedema, prolonged withdrawal, variceal rupture, and aspiration pneumonia; fatalities have occurred.[5] Modified-release injectable formulations of naltrexone are generally reserved for maintaining abstinence, see Maintenance, p. 1565.3.

1. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. *JAMA* 1998; 279: 229–34.
2. Gowing L, *et al.* Opioid antagonists with minimal sedation for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 12/08/10).
3. Gowing L, *et al.* Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 12/08/10).
4. Collins ED, *et al.* Anesthesia-assisted *vs* buprenorphine- or clonidine-assisted heroin detoxification and naltrexone induction: a randomized trial. *JAMA* 2005; 294: 903–13.
5. Hamilton RJ, *et al.* Complications of ultrarapid opioid detoxification with subcutaneous naltrexone pellets. *Acad Emerg Med* 2002; 9: 63–8.

Pruritus. For reference to the use of opioid antagonists, including naltrexone, in pruritus, see under Nalmefene, p. 1562.1.

Adverse Effects

For general adverse effects of opioid antagonists, see Naloxone, p. 1564.2.

Other adverse effects reported with naltrexone include oedema, increased or decreased appetite, ejaculatory difficulties and reduced potency, toothache, and depression and suicidal ideation. There have been reports of respiratory, urinary, and gastrointestinal infections. Nasopharyngitis, nasal congestion or bleeding, sneezing, hoarseness, cough, pupillary constriction, and tinnitus have been associated with naltrexone, as have rash, pruritus, acne, alopecia, and speech disorders. Reversible idiopathic thrombocytopenia purpura has been reported rarely.

High doses of naltrexone may cause hepatocellular injury. Hepatitis, abnormalities in hepatic function, and increases in liver enzymes or bilirubin have been reported. Urinary retention, increased frequency, or discomfort during urination have occurred.

Injection site reactions, including abscesses and tissue necrosis, have been reported with intramuscular naltrexone. There have also been rare reports of eosinophilic pneumonia.

Effects on the liver. Increased liver enzyme values were reported in 6 of 40 obese patients given naltrexone 50 or 100 mg daily for 8 weeks.[1] Five of the 6 patients had minimally abnormal liver function before naltrexone was given and liver function tests returned to baseline values or better on stopping naltrexone.

Raised transaminase levels were noted in 5 of 26 obese patients after 3 weeks of treatment with naltrexone 300 mg daily; transaminase activity returned to normal when treatment was stopped.[2]

1. Atkinson RL, *et al.* Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; 38: 419–22.
2. Mitchell JE. Naltrexone and hepatotoxicity. *Lancet* 1986; i: 1215.

Effects on the muscles. Asymptomatic rhabdomyolysis has been reported[1] in a patient receiving naltrexone; the condition resolved when naltrexone was withdrawn.

1. Zaim S, *et al.* Rhabdomyolysis associated with naltrexone. *Ann Pharmacother* 1999; 33: 312–3.

Precautions

Naltrexone should be avoided in patients physically dependent on opioids as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p. 109.1). Withdrawal symptoms may develop within 5 minutes and last up to 48 hours. Patients should be warned that attempting to overcome opioid antagonism may result in opioid intoxication or overdose; they may also be more sensitive to lower doses of opioids after treatment with naltrexone. For further precautions when using naltrexone as an adjunct in the treatment of opioid dependence, see Uses and Administration, p. 1565.2.

Therapeutic use of opioids should be avoided during naltrexone treatment. When analgesia is required, larger than usual doses of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects. Naltrexone should be stopped 48 to 72 hours before elective surgery involving opioid analgesia.

Naltrexone should be used with caution in patients with hepatic impairment and is contra-indicated in patients with acute hepatitis or hepatic failure. Regular monitoring of hepatic function is recommended. Caution is also advised in renal impairment.

Naltrexone may cross-react with some immunoassay methods for the detection of opioids in the urine.

Breast feeding. Naltrexone and its metabolite, 6-β-naltrexol, were detected in the breast milk of a mother taking oral naltrexone for opioid addiction. The total relative infant dose over 24 hours was calculated as 1.06%. A very low concentration of 6-β-naltrexol was found in the plasma of the infant, who was healthy and showed no adverse effects at 6 weeks.[1]

1. Chan CF, *et al.* Transfer of naltrexone and its metabolite 6,beta-naltrexol into human milk. *J Hum Lact* 2004; 20: 322–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naltrexone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Pregnancy. There are reports[1] of naltrexone use in pregnant women, either orally or as an implant. Although follow-up of the infants was not always undertaken, delivery of healthy infants was described in many cases.

1. Farid WO, *et al.* The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol* 2008; 6: 125–50.

Pharmacokinetics

Naltrexone is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism and may undergo enterohepatic recycling. It is extensively metabolised in the liver and the major metabolite, 6-β-naltrexol, may also possess weak opioid antagonist activity. Peak plasma concentrations of naltrexone and 6-β-naltrexol occur about 1 hour after oral dosing. The elimination half-life of oral naltrexone is around 4 hours and that of 6-β-naltrexol about 13 hours. Plasma concentrations of a modified-release formulation of naltrexone (*Vivitrol, USA*) peak about 2 hours after intramuscular injection. This is followed by another peak around 2 to 3 days later, and then a slow decline in concentrations from about 14 days post-dose to at least 1 month. The elimination half-life of both naltrexone and 6-β-naltrexol from this formulation is about 5 to 10 days. Naltrexone is about 20% bound to plasma proteins at therapeutic doses. Naltrexone and its metabolites are excreted mainly in the urine, with a small fraction in the faeces. Less than 2% of an oral dose of naltrexone is excreted unchanged.

Hepatic impairment. A study[1] in 11 patients with hepatic cirrhosis found that the systemic availability of naltrexone was significantly increased, particularly in those with decompensated disease.

1. Bertolotti M, *et al.* Effect of liver cirrhosis on the systemic availability of naltrexone in humans. *J Hepatol* 1997; 27: 505–511.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Revez; *Austral.*: Revia; *Austria*: Dependex; Ethylex; Naltrexin†; Nemexin†; Revia; *Belg.*: Nalorex; *Braz.*: Revia; *Canad.*: Revia; *Chile*: Nalerona; *China*: Narcoral (纳克莱); Nuo Xin Sheng (诺欣生); *Cz.*: Adepend; Nemexin†; Revia; *Denm.*: Adepend; *Fin.*: Revia; *Fr.*: Nalorex†; Revia; *Ger.*: Adepend; Nemexin; *Gr.*: Nalorex; *Hong Kong*: Revia†; *Hung.*: Antaxon; Nemexin†; Revia†; *India*: Naltima; Nodict; *Indon.*: Nutrexon; Phaltrexia†; *Irl.*: Ethylex; Nalorex; Revia†; *Ital.*: Antaxone; Nalorex; Narcoral; *Malaysia*: Narpan; *Mex.*: Revia†; *Neth.*: Nalorex†; Revia; *Norw.*: Revia†; *NZ*: Naltraccord; Revia; *Port.*: Antaxone; Basinal; Destoxican; Nalorex†; *Rus.*: Antaxone (Антаксон); Prodetoxon (Продетоксон); Vivitrol (Вивитрол); *Singapore*: Trexan; *Spain*: Antaxone; Celupan†; Revia; *Swed.*: Revia†; *Switz.*: Naltrexin; Nemexin†; *Thai.*: Revia; *Turk.*: Ethylex; *UK*: Adepend; Nalorex; Opizone; *Ukr.*: Antaxone (Антаксон); *USA*: Revia; Trexan; Vivitrol.

Multi-ingredient Preparations.

Used as an adjunct in:. *USA*: Embeda.

Pharmacopoeial Preparations
USP 36: Naltrexone Hydrochloride Tablets.

Obidoxime Chloride *(USAN, rINN)*

Chlorek Obidoksymu; Cloruro de obidoxima; LüH6; Obidoxim Chlorid; Obidoxima, cloruro de; Obidoximchlorid; Obidoxime, Chlorure d'; Obidoximi Chloridum; Обидоксима Хлорид.

1,1'-[Oxybis(methylene)]bis[4-(hydroxyimino)methyl]pyridinium dichloride.

$C_{14}H_{16}Cl_2N_4O_3$=359.2

CAS — 7683-36-5 (obidoxime); 114-90-9 (obidoxime chloride).

ATC — V03AB13.

ATC Vet — QV03AB13.

UNII — 3HXR312Z9M.

Profile

Obidoxime chloride is a cholinesterase reactivator with similar actions and uses to pralidoxime (p. 1571.1). It is given with atropine in the treatment of organophosphorus poisoning in a usual initial dose of 250 mg (4 mg/kg) by slow intravenous injection or by intramuscular injection. This may be followed by intravenous infusion of 750 mg over 24 hours, continued until the concentration of organophosphate is below critical levels; alternatively, repeated doses of 4 to 8 mg/kg by intravenous injection may be given at intervals of 2 to 4 hours. For doses in children, see below.

References.

1. Thiermann H, *et al.* Cholinesterase status, pharmacokinetics and laboratory findings during obidoxime therapy in organophosphate poisoned patients. *Hum Exp Toxicol* 1997; 16: 473–80.
2. Eyer F, *et al.* Obidoxime in acute organophosphate poisoning: 1—clinical effectiveness. *Clin Toxicol* 2009; 47: 798–806.
3. Thiermann H, *et al.* Obidoxime in acute organophosphate poisoning: 2—PK/PD relationships. *Clin Toxicol* 2009; 47: 807–13.
4. Thiermann H, *et al.* Pharmacokinetics of obidoxime in patients poisoned with organophosphorus compounds. *Toxicol Lett* 2010; 197: 236–42.

Administration in children. Obidoxime chloride is used with atropine to treat children with organophosphorus poisoning. An initial dose of 4 to 8 mg/kg (maximum 250 mg) by slow intravenous injection or by intramuscular injection is followed by either a continuous intravenous infusion of 10 mg/kg daily, or repeated doses of 4 to 8 mg/kg by intravenous injection at intervals of 2 to 4 hours.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies obidoxime as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/08/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Toxogonin†; *Chile*: Toxogonin; *Cz.*: Toxogonin; *Ger.*: Toxogonin; *Neth.*: Toxogonin; *S. Afr.*: Toxogonin; *Switz.*: Toxogonine.

Penicillamine *(BAN, USAN, rINN)*

Penicilamin; Penicilamina; Penicilaminas; Penicillamin; Penicillamina; D-Penicillamine; Pénicillamine; Penicillaminum; Penicylamina; Penisilamin; Penisilaminii; Пеницилламин.

D-3,3-Dimethylcysteine; D-3-Mercaptovaline.

$C_5H_{11}NO_2S$=149.2

CAS — 52-67-5 (penicillamine); 2219-30-9 (penicillamine hydrochloride).

ATC — M01CC01.

ATC Vet — QM01CC01.

UNII — GNN1DV99GX.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Penicillamine). A white or almost white, crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 5.5.

USP 36: (Penicillamine). A white or practically white, crystalline powder having a slight characteristic odour. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 1% solution in water is between 4.5 and 5.5. Store in airtight containers.

Uses and Administration

Penicillamine is a chelator that aids the elimination from the body of certain heavy-metal ions, including copper, lead, and mercury, by forming stable water-soluble complexes with them that are readily excreted by the kidney. It is used in the treatment of Wilson's disease (below) to promote the excretion of copper, in heavy-metal poisoning such as lead poisoning (p. 2542.1), in cystinuria (below) to reduce urinary concentrations of cystine, in severe active rheumatoid arthritis (p. 13.2), and in chronic active hepatitis.

Penicillamine is given orally and should be taken on an empty stomach. To reduce toxicity, the lowest effective dose should be used.

In the treatment of **Wilson's disease**, the optimal dosage to achieve a negative copper balance should be determined initially by measuring 24-hour urinary copper excretion: a 24-hour cupriuresis of over 2 mg should be sustained for about 3 months. Subsequently, free copper in the serum is monitored; adequately treated patients will usually have free-copper serum values of less than 10 micrograms per 100 mL. In the UK, an initial dose of 1.5 to 2 g daily in divided doses is suggested; a maintenance dose of 0.75 to 1 g daily may be adequate once control is achieved and should be continued indefinitely. A maintenance dose of 2 g daily should not be continued for more than a year. A dose of 20 mg/kg daily in divided doses is suggested for the elderly. In the USA, a usual initial dose of 0.75 to 1.5 g daily is suggested; it is seldom necessary to exceed 2 g daily. In those who cannot tolerate such doses an initial dose of 250 mg daily, increased gradually, may provide better control and reduce adverse effects.

In the management of **lead poisoning**, penicillamine may be given in doses of 1 to 1.5 g daily in divided doses until urinary lead is stabilised at less than 500 micrograms/day. Elderly patients may be given 20 mg/kg daily in divided doses.

In **cystinuria**, doses of penicillamine are adjusted according to cystine concentrations in the urine. For the *treatment* of cystinuria and cystine calculi, the dose is usually in the range of 1 to 4 g daily in divided doses to achieve a urinary cystine concentration of not more than 200 mg/litre. An initial dose of 250 mg daily increased gradually may provide good control and reduce adverse effects. For the *prevention* of cystine calculi, doses of 0.5 to 1 g at bedtime may be given to achieve a urinary cystine concentration of not more than 300 mg/litre. An adequate fluid intake is essential to maintain urine flow when penicillamine is used for cystinuria.

In the treatment of **severe active rheumatoid arthritis**, an initial dose of penicillamine 125 to 250 mg daily is increased gradually by the same amount at intervals of 4 to 12 weeks. Remission is usually achieved with maintenance doses of 500 to 750 mg daily in divided doses, but up to 1.5 g daily may be required. Improvement may not occur for several months; US licensed product information suggests that penicillamine should be stopped if there is no response after treatment for 3 to 4 months with 1 to 1.5 g daily; in the UK, treatment should be stopped if there is no benefit within 12 months. After remission has been sustained for 6 months an attempt may be made to gradually reduce the dose by 125 to 250 mg daily every 3 months but relapse may occur. Lower doses may be required in the elderly who may be more susceptible to developing adverse effects. Initial doses of 125 mg daily are recommended, gradually increased by this amount every 4 to 12 weeks to a maximum of 1 g daily if necessary.

In the management of **chronic active hepatitis**, penicillamine may be given after liver function tests have indicated that the disease has been controlled by corticosteroids. The initial dose is 500 mg daily in divided doses, increased gradually over 3 months to 1.25 g daily, while at the same time reducing the corticosteroid dose.

For doses in children, see below.

Acetylpenicillamine has been used in mercury poisoning.

Administration in children. Penicillamine is used in children for the treatment of Wilson's disease, for poisoning by heavy metals such as lead, for cystinuria, and for severe active juvenile rheumatoid arthritis.

For the treatment of **Wilson's disease**, an oral dose of 20 mg/kg daily in 2 or 3 divided doses is recommended. Children from 12 years may be given the adult maintenance dose, see above.

For **lead poisoning**, the recommended daily oral dose is 15 to 20 mg/kg in 2 or 3 divided doses in children whose blood lead concentrations are less than 45 micrograms/100 mL.

In **cystinuria**, the penicillamine dose should be adjusted to maintain the urinary cystine concentration below 200 mg/litre and adequate fluid intake ensured. An oral dose of 20 to 30 mg/kg daily in 2 or 3 divided doses has been suggested.

For **juvenile idiopathic arthritis**, UK licensed product information recommends an initial oral dose of penicillamine 2.5 to 5 mg/kg daily before food, increased every 4 weeks over 3 to 6 months to a usual maintenance dose of 15 to 20 mg/kg daily, although the *BNFC* advises that penicillamine is no longer used as a disease-modifying antirheumatic drug.

Chronic active hepatitis. Penicillamine has been tried in chronic active hepatitis (p. 1602.3) as an alternative to prolonged corticosteroid maintenance therapy once control of the disease is achieved. The dose of penicillamine is increased over several months to a suitable maintenance dose and, at the same time, the corticosteroid dose is decreased.

Cystinuria. Cystinuria is an inherited disorder of renal amino-acid excretion in which there is excessive excretion of cystine (cysteine disulfide), along with ornithine, lysine, and arginine. The low solubility of cystine leads to the formation of cystine stones in the urinary tract, resulting in pain, haematuria, renal obstruction, infection, and renal impairment.[1,2] Treatment is mainly aimed at reducing the urinary concentration of cystine to below its solubility limit of about 300 mg/litre at urinary pH (5 to 7). Patients with cystinuria excrete 400 to 1200 mg cystine daily and should be advised to drink at least 3 litres of water daily, including at night, to maintain a dilute urine. Cystine is more soluble in alkaline urine (above 7.5) and urinary alkalinisers such as potassium bicarbonate or potassium citrate may be used; sodium-based alkalinisers are not generally recommended. Penicillamine may also be used, particularly in patients where these measures are ineffective or not tolerated; it complexes with cystine to form more soluble compounds, thereby preventing cystine stone formation, and promoting the gradual dissolution of existing stones. Adverse effects are common and tiopronin, which has a similar action, may be used as an alternative. Captopril may increase the solubility of cystine and has been used in some patients such as those with hypertension, although evidence of efficacy is inconsistent. Dietary restrictions have also been used: a reduction in sodium reduces urinary cystine excretion and a low-salt diet is recommended. Restriction of protein, to reduce methionine, a precursor of cystine, has also been suggested, but is not generally recommended as it is difficult to maintain. Urological interventions may be necessary to remove established stones.[1-3]

1. Ahmed K, *et al.* Cystine calculi: challenging group of stones. *Postgrad Med J* 2006; **82**: 799–801.
2. Knoll T, *et al.* Cystinuria in childhood and adolescence: recommendations for diagnosis, treatment, and follow-up. *Pediatr Nephrol* 2005; **20**: 19–24.
3. Türk C, *et al.* European Association of Urology. Guidelines on urolithiasis (updated April 2010). Available at: http://www.uroweb.org/gls/pdf/Urolithiasis%202010.pdf (accessed 18/03/11)

Primary biliary cirrhosis. Copper accumulation in the liver has been noted in patients with primary biliary cirrhosis (see under Ursodeoxycholic Acid, p. 2638.3) and therapy with penicillamine to reduce liver-copper concentrations has been studied. Despite good preliminary results, most studies have found it to be ineffective and any benefit appears to be offset by the high incidence of adverse effects.[1,2]

1. James OFW. D-Penicillamine for primary biliary cirrhosis. *Gut* 1985; **26**: 109–13.
2. Gong Y, *et al.* D-penicillamine for primary biliary cirrhosis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 18/03/11).

Retinopathy of prematurity. Penicillamine has been investigated for the prophylaxis of retinopathy of prematurity (p. 2120.3) in infants considered to be at risk, and a systematic review of 2 such studies considered that there was evidence for a reduced incidence of acute retinopathy.[1] Further studies were considered justified, with careful attention to possible adverse effects.

1. Phelps D, *et al.* D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2001 (accessed 18/03/11).

Rheumatoid arthritis. Penicillamine is one of a diverse group of disease-modifying antirheumatic drugs that have been used in rheumatoid arthritis (p. 13.2) in an attempt to suppress the rate of cartilage erosion or alter the course of the disease. However, early enthusiasm for penicillamine has been tempered by a high incidence of adverse effects.[1] During long-term therapy as many as 50% of patients taking penicillamine have been reported to stop treatment because of adverse effects.[2] Low doses of penicillamine to reduce the incidence of adverse effects have been tried and while doses as low as 125 mg daily have been claimed to be effective in some patients, a 36-week multicentre double-blind study[3] involving 225 patients concluded that a dose of penicillamine 500 mg daily was only slightly more effective than placebo. A dose of 125 mg daily was not significantly different from either the 500-mg dose or placebo. However, a 5-year open study[4] comparing penicillamine in doses up to 500 mg daily with hydroxychloroquine, sodium aurothiomalate, or auranofin found penicillamine to be as effective as the other drugs and well tolerated, with 53% of the patients randomised to penicillamine still receiving it at 5 years, as opposed to about 30 to 35% of those randomised to other drugs.

1. Suarez-Almazor ME, *et al.* Penicillamine for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 31/03/11).
2. Moens HJB, *et al.* Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; **14**: 1115–19.
3. Williams HJ, *et al.* Low-dose D-penicillamine therapy in rheumatoid arthritis: a controlled, double-blind clinical trial. *Arthritis Rheum* 1983; **26**: 581–92.
4. Jessop JD, *et al.* A long-term five-year randomized controlled trial of hydroxychloroquine, sodium aurothiomalate, auranofin and penicillamine in the treatment of patients with rheumatoid arthritis. *Br J Rheumatol* 1998; **37**: 992–1002.

Scleroderma. Penicillamine affects the cross-linking of collagen,[1] and observational studies[2,3] have suggested that it may be of benefit in scleroderma (p. 1938.3), and perhaps in some visceral manifestations of systemic sclerosis. A randomised study[4] comparing a conventional dose of penicillamine (up to 1 g daily) with a very low dose (125 mg on alternate days) found no difference in outcome, but there were more adverse effects with the higher dose. Although the lower dose was not expected to be effective, the skin score improved significantly in both groups; however, there was insufficient evidence to attribute this to use of penicillamine, and its role in scleroderma remains to be established.

For a report of sclerodermatous lesions in a patient taking penicillamine for Wilson's disease, see Scleroderma, under Effects on the Skin, p. 1569.2.

1. Herbert CM, *et al.* Biosynthesis and maturation of skin collagen in scleroderma, and effect of D-penicillamine. *Lancet* 1974; **i**: 187–92.
2. Steen VD, *et al.* D-Penicillamine therapy in progressive systemic sclerosis (scleroderma): a retrospective analysis. *Ann Intern Med* 1982; **97**: 652–9.
3. Derk CT, *et al.* A retrospective randomly selected cohort study of D-penicillamine treatment in rapidly progressive diffuse cutaneous systemic sclerosis of recent onset. *Br J Dermatol* 2008; **158**: 1063–8.
4. Clements PJ, *et al.* High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999; **42**: 1194–1203.

Wilson's disease. Wilson's disease, or hepatolenticular degeneration, is a rare autosomal disorder of copper accumulation.[1-7] Excretion of excess copper, which normally occurs via the bile, is impaired and total body copper progressively increases. The excess copper accumulates in the liver, brain, and other organs including the kidneys and corneas, and eventually causes tissue damage.

Effective treatment of Wilson's disease involves the use of copper-reducing drugs to establish a negative copper balance. This prevents deposition of more copper and also mobilises excess copper that has already been deposited making it available for excretion. Once negative copper balance has been achieved, maintenance treatment must be continued lifelong. Dietary restriction of copper is not generally considered to be an important part of the treatment of Wilson's disease, although patients may be advised to avoid copper-rich foods, such as liver and shellfish, during the first year of treatment and to restrict their consumption thereafter. Symptomatic recovery from copper overload occurs slowly, but is usually complete if treatment is started early enough, and a normal life expectancy can be achieved. However, once irreversible

organ damage such as liver cirrhosis has occurred, treatment can only prevent further deterioration; those presenting with end-stage liver disease do not benefit from copper-reducing therapy, and liver transplantation is necessary (although successful medical treatment has been reported in children). The drugs used to reduce copper concentrations in the treatment of Wilson's disease are penicillamine, trientine, and zinc. Dimercaprol has been used with penicillamine in refractory patients. Ammonium tetrathiomolybdate, an investigational drug, may also be used.

- *Penicillamine* reduces copper concentrations in several ways. Its main action is to chelate circulating copper, which is then excreted in the urine. In addition, penicillamine reduces the affinity of copper for proteins and polypeptides, allowing removal of copper from tissues. It also induces hepatic synthesis of metallothionein, a protein that combines with copper to form a non-toxic product.
- *Trientine* is a less potent copper chelator than penicillamine; it competes for copper bound to serum albumin and increases copper excretion.
- *Zinc* induces synthesis of metallothionein in the intestine so that absorption of copper from the gastrointestinal tract is blocked. It is usually given as the acetate as this form is less irritating to the stomach than the sulfate.
- *Ammonium tetrathiomolybdate* forms a complex with protein and copper. When it is given with food it blocks the intestinal absorption of copper, and when taken between meals it combines with albumin- and caeruloplasmin-bound copper.
- *Dimercaprol* may accelerate the removal of copper from brain tissue as it is not electrically charged and therefore crosses vascular and cellular membranes more readily than penicillamine, which has charged carboxyl and amino groups.

CHOICE OF DRUG. Penicillamine is generally regarded as the drug of choice for the initial management of Wilson's disease as it produces a rapid reduction in copper levels. However, it may initially exacerbate neurological symptoms (possibly due to transiently increased brain and blood copper concentrations) and some practitioners therefore suggest starting with zinc; zinc is less suitable in those requiring rapid reduction of copper levels as it has a slow onset of action. Trientine, which may also exacerbate neurological symptoms, is mainly used in patients intolerant of penicillamine, although it is also used for initial treatment as there is less toxicity. Ammonium tetrathiomolybdate is under investigation for the initial reduction of copper levels; it may be particularly suitable for patients with neurological symptoms. Dimercaprol can be used with penicillamine in patients who remain symptomatic or deteriorate on penicillamine alone. Because it must be given intramuscularly it is usually used in acute disease to improve control.

Once a negative copper balance is achieved, maintenance therapy must be continued for life. Penicillamine, trientine, and zinc are all used for maintenance treatment. Patients taking penicillamine are also given pyridoxine to prevent deficiency (see Precautions, p. 1569.3). The adverse effects of penicillamine may be a problem during long-term use and zinc, which has low toxicity, is often preferred. Zinc is also used in patients in the asymptomatic stage of the disease.

1. Brewer GJ. Recognition, diagnosis, and management of Wilson's disease. *Proc Soc Exp Biol Med* 2000; 223: 39–46.
2. Roberts EA, Schilsky ML. A practice guideline on Wilson disease. *Hepatology* 2003; 37: 1475–92.
3. El-Youssef M. Wilson disease. *Mayo Clin Proc* 2003; 78: 1126–36.
4. Merle U, *et al.* Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study. *Gut* 2007; 56: 115–20.
5. Ala A, *et al.* Wilson's disease. *Lancet* 2007; 369: 397–408.
6. Lee V, *et al.* Wilson's disease: a complex picture. *Clin Pharmacist* 2009; 1: 239–41.
7. Lorincz MT. Neurologic Wilson's disease. *Ann N Y Acad Sci* 2010; 1184: 173–87.

Adverse Effects and Treatment

Adverse effects occur frequently with penicillamine and may be severe. Gastrointestinal disturbances including anorexia, nausea, and vomiting may occur; oral ulceration and stomatitis have been reported, as has transient loss or impairment of taste.

Rashes occurring early in treatment are commonly allergic and may be associated with pruritus, urticaria, and fever; they are usually transient but temporary withdrawal or dose reduction and use of corticosteroids or antihistamines may be required. Penicillamine treatment should be permanently stopped if a rash develops with fever, arthralgia, and lymphadenopathy. Dermatomyositis, lupus erythematosus, and pemphigus have been reported. Stevens-Johnson syndrome and toxic epidermal necrolysis have been seen during penicillamine treatment. Prolonged use of high doses may affect skin collagen and elastin, resulting in increased skin friability, extravasation of blood, pseudoxanthoma elasticum, and eruptions resembling elastosis perforans serpiginosa. A late rash or acquired epidermolysis bullosa (penicillamine dermatopathy) has occurred and may require doses to be reduced or stopped.

Haematological adverse effects have included thrombocytopenia, neutropenia, and leucopenia; these are usually reversible, but agranulocytosis and aplastic anaemia have occurred and fatalities have been reported. Treatment may need to be withheld or withdrawn if leucopenia or thrombocytopenia occur, or if there are 3 successive falls in the white blood cell or platelet count while still within the usual range. Other adverse effects on the blood include haemolytic or sideroblastic anaemia, thrombotic thrombocytopenia purpura, red cell aplasia, monocytosis, leucocytosis, eosinophilia, and thrombocytosis.

Proteinuria occurs frequently and in some patients may progress to glomerulonephritis or nephrotic syndrome; renal failure has been reported, and Goodpasture's syndrome (glomerulonephritis associated with intra-alveolar haemorrhage) has been fatal. Treatment should be immediately withdrawn if there are abnormal urinary findings with haemoptysis and pulmonary infiltrates. Penicillamine-induced haematuria is rare; treatment may need to be withdrawn for increasing or persistent proteinuria or haematuria.

Effects on the nervous system include psychiatric disturbances, agitation, anxiety, visual disturbances, tinnitus, optic neuritis, and sensory or motor peripheral neuropathies including Guillain Barré syndrome; muscular weakness may occur with the peripheral neuropathies.

Other adverse effects associated with penicillamine include breast-enlargement, alopecia, yellow nail syndrome, reactivated peptic ulcer, hypoglycaemia associated with anti-insulin antibodies, myasthenic syndrome that is usually reversible but has progressed to fatal myasthenia gravis, polymyositis, increases in liver enzyme values, intrahepatic cholestasis and toxic hepatitis, pancreatitis, vasculitis including fatal renal vasculitis, thyroiditis, migratory polyarthralgia, rheumatoid arthritis, or septic arthritis in those with pre-existing rheumatoid arthritis, pulmonary fibrosis, allergic alveolitis, obliterative bronchiolitis, interstitial pneumonitis, and asthma.

Incidence of adverse effects. References describing the range and incidence of adverse effects associated with of D-penicillamine.[1-3] The L- or DL-forms are much more toxic.[4]

1. Kean WF, *et al.* Efficacy and toxicity of D-penicillamine for rheumatoid disease in the elderly. *J Am Geriatr Soc* 1982; 30: 94–100.
2. Steen VD, *et al.* The toxicity of D-penicillamine in systemic sclerosis. *Ann Intern Med* 1986; 104: 699–705.
3. Munro R, Capell HA. Penicillamine. *Br J Rheumatol* 1997; 36: 104–9.
4. Kean WF, *et al.* Chirality in antirheumatic drugs. *Lancet* 1991; 338: 1565–8.

Effects on the blood. Of the 18 deaths ascribed to penicillamine reported to the UK CSM between January 1964 and December 1977, 14 were apparently due to blood disorders, at least 7 of them being marrow aplasias. The myelotoxicity of penicillamine was reviewed in 10 patients with confirmed or suspected marrow depression during penicillamine treatment for rheumatoid arthritis or scleroderma; 6 died.[1]

An incidence of 12 to 27% has been reported for penicillamine-induced thrombocytopenia in patients with rheumatoid arthritis, possibly due to bone-marrow suppression and a reduced platelet-production rate.[2]

There have been isolated reports[3-5] of thrombotic thrombocytopenic purpura attributed to the use of penicillamine, with some fatalities.

1. Kay AGL. Myelotoxicity of D-penicillamine. *Ann Rheum Dis* 1979; 38: 232–6.
2. Thomas D, *et al.* Thrombokinetics in patients with rheumatoid arthritis treated with D-penicillamine. *Ann Rheum Dis* 1984; 43: 402–6.
3. Ahmed P, *et al.* Thrombohemolytic thrombocytopenic purpura during penicillamine therapy. *Arch Intern Med* 1978; 138: 1292–3.
4. Speth PAJ, *et al.* Thrombotic thrombocytopenic purpura associated with D-penicillamine treatment in rheumatoid arthritis. *J Rheumatol* 1982; 9: 812–13.
5. Trice JM, *et al.* Thrombotic thrombocytopenic purpura during penicillamine therapy in rheumatoid arthritis. *Arch Intern Med* 1983; 143: 1487–8.

Effects on the breasts. Breast enlargement has been reported both in women[1-5] and in men[6] taking penicillamine and may be a rare adverse effect. In some patients breast enlargement was prolonged with poor resolution, and others required surgery. Danazol has been used successfully to treat penicillamine-induced breast gigantism.[2-4]

1. Thew DCN, Stewart IM. D penicillamine and breast enlargement. *Ann Rheum Dis* 1980; 39: 200.
2. Taylor PJ, *et al.* Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; 282: 362–3.
3. Rooney PJ, Cleland J. Successful treatment of D-penicillamine-induced breast gigantism with danazol. *BMJ* 1981; 282: 1627–8.
4. Craig HR. Penicillamine induced mammary hyperplasia: report of a case and review of the literature. *J Rheumatol* 1988; 15: 1294–7.
5. Tchebiner JZ. Breast enlargement induced by D-penicillamine. *Ann Pharmacother* 2002; 36: 444–5.
6. Reid DM, *et al.* Reversible gynaecomastia associated with D-penicillamine in a man with rheumatoid arthritis. *BMJ* 1982; 285: 1083–4.

Effects on endocrine function. Congenital goitrous hypothyroidism was reported in 2 siblings whose mother took penicillamine during pregnancy for Wilson's disease. Subclinical hypothyroidism was also noted in a further 5 children with Wilson's disease, 4 of whom had taken penicillamine for 3 to 3.5 years and then changed to zinc therapy; zinc was the sole treatment in 1 patient. During penicillamine therapy, thyroid-stimulating hormone concentrations were significantly higher than those during zinc treatment. The authors suggested hypothyroidism could have been the result of inhibition of thyroperoxidase activity by penicillamine.[1]

1. Hanukoglu A, *et al.* Hypothyroidism and dyshormonogenesis induced by D-penicillamine in children with Wilson's disease and healthy infants born to a mother with Wilson's disease. *J Pediatr* 2008; 153: 864–6.

Effects on the gastrointestinal tract. There have been isolated reports of acute colitis in patients taking penicillamine.[1,2] Ileal ulceration and stenosis in a patient with Wilson's disease was considered to be related to elastosis probably resulting from long-term penicillamine therapy.[3]

1. Hickling P, Fuller J. Penicillamine causing acute colitis. *BMJ* 1979; 2: 367.
2. Grant GB. Penicillamine causing acute colitis. *BMJ* 1979; 2: 555.
3. Wassef M, *et al.* Unusual digestive lesions in a patient with Wilson's disease treated with long-term penicillamine. *N Engl J Med* 1985; 313: 49.

Effects on the heart. For reports of heart block, Stokes-Adams syndrome, and fatal myocarditis in patients taking penicillamine, see Polymyositis under Effects on the Muscles and the Neuromuscular System, p. 1569.1.

Effects on the kidneys. Proteinuria associated with penicillamine[1,2] has usually occurred within 4 to 18 months of starting therapy, although onset can be later. A greater incidence has been found in patients with rheumatoid arthritis and cystinuria than in those with Wilson's disease. The severity varies; proteinuria of nephrotic proportions usually develops rapidly but resolves on drug withdrawal. Minimal change, mesangioproliferative, and membranous nephropathy have all been associated with penicillamine; progressive glomerulonephritis has been seen in a few patients with features of Goodpasture's syndrome (see Effects on the Respiratory System, p. 1569.1).

Although there is some evidence of a relationship between nephropathy and penicillamine dose and its rate of increase,[1] a study of 33 rheumatoid arthritis patients with penicillamine-induced nephropathy found no correlation with the dose or duration of treatment.[3] Appreciable proteinuria could still be detected 12 months after stopping penicillamine in 40% of these patients, but subsequently resolved in those whose proteinuria was solely related to penicillamine.

Penicillamine was successfully reintroduced and continued for at least 13 months in 5 patients with rheumatoid arthritis who had developed proteinuria during the first course of therapy. Proteinuria did not recur.[4] Another study[5] in 8 patients with proteinuria but no oedema suggested that penicillamine could be safely continued; proteinuria resolved in 5 of the patients during continued therapy.

Corticosteroids have been used in patients developing rapidly progressive glomerulonephritis[6] but may be unnecessary and potentially hazardous in patients who develop nephrotic syndrome.[3]

1. Anonymous. Penicillamine nephropathy. *BMJ* 1981; 282: 761–2.
2. Habib GS, *et al.* Penicillamine and nephrotic syndrome. *Eur J Intern Med* 2006; 17: 343–8.
3. Hall CL, *et al.* Natural course of penicillamine nephropathy: a long term study of 33 patients. *BMJ* 1988; 296: 1083–6.
4. Hill H, *et al.* Resumption of treatment with penicillamine after proteinuria. *Ann Rheum Dis* 1979; 38: 229–31.
5. DeSilva RN, Eastmond CJ. Management of proteinuria secondary to penicillamine therapy in rheumatoid arthritis. *Clin Rheumatol* 1992; 11: 216–9.
6. Ntoso KA, *et al.* Penicillamine-induced rapidly progressive glomerulonephritis in patients with progressive systemic sclerosis: successful treatment of two patients and a review of the literature. *Am J Kidney Dis* 1986; 8: 159–63.

Effects on the liver. Penicillamine has been associated with hepatotoxicity. A case report and review of the literature[1] described 9 patients, all of whom had liver function profiles consistent with intrahepatic cholestasis; 1 patient died of acute renal failure but the others improved rapidly after drug withdrawal. In a later report,[2] a 72-year-old man with rheumatoid arthritis developed jaundice about 4 weeks after starting penicillamine therapy. Liver biopsy indicated a slight degree of cholangitis with eosinophils in the portal tracts and severe predominantly intrahepatocellular cholestasis. Jaundice cleared within 3 weeks of stopping penicillamine and liver enzyme values approached normal after 6 weeks. However, in another case[3] cholestasis persisted despite withdrawal of penicillamine and the patient died of sepsis 14 months later. Monitoring of

liver function and eosinophil counts in the early weeks of penicillamine therapy has been recommended.[1]

1. Seibold JR, *et al.* Cholestasis associated with D-penicillamine therapy: case report and review of the literature. *Arthritis Rheum* 1981; 24: 554–6.
2. Devogelaer JP, *et al.* A case of cholestatic hepatitis associated with D-penicillamine therapy for rheumatoid arthritis. *Int J Clin Pharmacol Res* 1985; 5: 35–8.
3. Jacobs JWG, *et al.* Fatal cholestatic hepatitis caused by D-penicillamine. *Br J Rheumatol* 1994; 33: 770–3.

Effects on the muscles and the neuromuscular system. Neuromyotonia,[1] and profound sensory and motor neuropathy that responded to pyridoxine supplementation,[2] have occurred in patients taking penicillamine. Low back pain with fever and rash has also been reported;[3] back pain and fever recurred on rechallenge. It was suggested that an allergic mechanism was involved.

1. Reeback J, *et al.* Penicillamine-induced neuromyotonia. *BMJ* 1979; 1: 1464–5.
2. Pool KD, *et al.* Penicillamine-induced neuropathy in rheumatoid arthritis. *Ann Intern Med* 1981; 95: 457–8.
3. Bannwarth B, *et al.* Low back pain associated with penicillamine. *BMJ* 1991; 303: 525.

MYASTHENIA. Myasthenia gravis is a well recognised, though uncommon, complication of long-term penicillamine therapy, particularly in patients with rheumatoid arthritis or other auto-immune disorders.[1–5] Symptoms are similar to those seen with spontaneous myasthenia gravis and include ptosis and diplopia, and generalised weakness, occasionally affecting the respiratory muscles. The onset of symptoms usually occurs within 6 to 7 months but may be delayed for several years. Myasthenic symptoms usually resolve spontaneously once penicillamine is withdrawn, but some patients require anticholinesterase therapy. Acetylcholine receptor antibodies have been reported in 75% or more of affected patients.[2,3] Several reports have suggested a genetic tendency to penicillamine-induced myasthenia, and an association with HLA antigens DR1 and Bw35 has been found in some studies,[1,4,6] although others[5] have not replicated these findings.

1. Delamere JP, *et al.* Penicillamine-induced myasthenia in rheumatoid arthritis: its clinical and genetic features. *Ann Rheum Dis* 1983; 42: 500–4.
2. Carter H, *et al.* La myasthénie au cours du traitement de la polyarthrite rhumatoïde par la D-pénicillamine. *Therapie* 1984; 39: 689–95.
3. Katz LJ, *et al.* Ocular myasthenia gravis after D-penicillamine administration. *Br J Ophthalmol* 1989; 73: 1015–18.
4. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; 286: 338–40.
5. Drosos AA, *et al.* D-penicillamine induced myasthenia gravis: clinical, serological and genetic findings. *Clin Exp Rheumatol* 1993; 11: 387–91.
6. Hill M, *et al.* T cell responses to D-penicillamine in drug-induced myasthenia gravis: recognition of modified DR1:peptide complexes. *J Neuroimmunol* 1999; 97: 146–53.

POLYMYOSITIS. Penicillamine therapy has been associated rarely with polymyositis and dermatomyositis.[1–7] Cardiac complications may occur: at least 2 deaths have resulted from myocarditis,[1] and complete heart block[1,3,8] and severe Stokes-Adams attacks[3] have been reported. It is possible that some patients may have a genetically determined susceptibility to this complication.[4]

1. Doyle DR, *et al.* Fatal polymyositis in D-penicillamine-treated rheumatoid arthritis. *Ann Intern Med* 1983; 98: 327–30.
2. Renier JC, *et al.* Polymyosite induite par la D-pénicillamine. *Therapie* 1984; 39: 697–703.
3. Christensen PD, Sørensen KB. Penicillamine-induced polymyositis with complete heart block. *Eur Heart J* 1989; 10: 1041–4.
4. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; 14: 995–1001.
5. Aydintug AO, *et al.* Polymyositis complicating D-penicillamine treatment. *Postgrad Med J* 1991; 67: 1018–20.
6. Jan V, *et al.* Pemphigus, polymyosite et myasthénie induits par la D-pénicillamine. *Ann Dermatol Venereol* 1999; 126: 153–6.
7. Dourmishev LA, *et al.* D-penicillamine induced polymyositis and morphea in a woman with Hashimoto thyroiditis. *J Eur Acad Dermatol Venereol* 2002; 16: 538–9.
8. Wright GD, *et al.* D-penicillamine induced polymyositis causing complete heart block. *Clin Rheumatol* 1994; 13: 80–2.

Effects on the respiratory system. Pulmonary haemorrhage associated with progressive renal failure has been reported[1,2] with penicillamine and has generally been classified as Goodpasture's syndrome, although patients usually lack anti-glomerular basement membrane antibodies; an immune-complex mechanism has also been suggested.[1] There have been rare reports of obliterative bronchiolitis in patients with rheumatoid arthritis treated with penicillamine.[3–6]

Upper respiratory tract disorders have also been reported. A 76-year-old patient taking penicillamine developed rhinitis, bilateral blepharitis, and pemphigus foliaceus;[7] the rhinitis and blepharitis resolved when penicillamine was withdrawn. In addition, 2 patients with lower respiratory symptoms also developed persistent sinusitis,[4] which required surgery.

1. Turner-Warwick M. Adverse reactions affecting the lung: possible association with D-penicillamine. *J Rheumatol* 1981; 8 (suppl 7): 166–8.
2. Derk CT, Jimenez SA. Goodpasture-like syndrome induced by D-penicillamine in a patient with systemic sclerosis: report and review of the literature. *J Rheumatol* 2003; 30: 1616–20.
3. Lyle WH. D-Penicillamine and fatal obliterative bronchiolitis. *BMJ* 1977; 1: 105.
4. Epler GR, *et al.* Bronchiolitis and bronchitis in connective tissue disease: a possible relationship to the use of penicillamine. *JAMA* 1979; 242: 528–32.
5. Murphy KC, *et al.* Obliterative bronchiolitis in two rheumatoid arthritis patients treated with penicillamine. *Arthritis Rheum* 1981; 24: 557–60.
6. Wolfe F, *et al.* Upper and lower airway disease in penicillamine treated patients with rheumatoid arthritis. *J Rheumatol* 1983; 10: 406–10.
7. Presley AP. Penicillamine induced rhinitis. *BMJ* 1988; 296: 1332.

Effects on the skin. Penicillamine-induced skin lesions have been reviewed.[1] Reactions include those resulting from interference with collagen and elastin (see below); those associated with auto-immune mechanisms such as pemphigus, pemphigoid, lupus erythematosus, and dermatomyositis; and those classified as acute sensitivity reactions including macular or papular eruptions and urticaria. The effects on collagen and elastin tend to occur only after prolonged use of high doses, as in patients with Wilson's disease or cystinuria, whereas patients with diseases characterised by altered immune systems, such as rheumatoid arthritis, are more prone to develop the antibody-related adverse skin reactions. Acute hypersensitivity reactions tend to occur early in treatment, usually within the first 7 to 10 days, and appear not to be dose-related. Lichenoid reactions, stomatitis, nail changes, and adverse effects on hair have also occurred.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; 8: 548–58.

INTERFERENCE WITH COLLAGEN AND ELASTIN. Long-term, high-dose treatment with penicillamine can interfere with elastin and collagen production giving rise to increased skin friability, haemorrhagic lesions, miliary papules, and excessive wrinkling and laxity of the skin.[1] Penicillamine dermatopathy, characterised by wrinkling and purpura over bony prominences, has been described.[2] In addition, lesions resembling pseudoxanthoma elasticum have been reported.[3,4]

Abnormal elastic tissue has also been reported in patients taking low doses of penicillamine (less than 1 g daily), not only in the skin but also in joint capsules,[5] and elastosis perforans serpiginosa (normally described after long-term, higher dose therapy[6,7]) has been reported.[8]

In all these cases, histological findings generally show damage to elastic fibres giving them a typical appearance described as 'lumpy-bumpy' or 'bramble-bush'.

For reports of cutis laxa in neonates, see Pregnancy under Precautions, p. 1570.1.

1. Levy RS, *et al.* Penicillamine: review and cutaneous manifestations. *J Am Acad Dermatol* 1983; 8: 548–58.
2. Sternlieb I, Scheinberg IH. Penicillamine therapy for hepatolenticular degeneration. *JAMA* 1964; 189: 748–54.
3. Thomas RHM, *et al.* Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1984; 77: 794–8.
4. Bentley-Phillips B. Pseudoxanthoma elasticum-like skin changes induced by penicillamine. *J R Soc Med* 1985; 78: 787.
5. Dalziel KL, *et al.* Elastic fibre damage induced by low-dose D-penicillamine. *Br J Dermatol* 1990; 123: 305–12.
6. Hill VA, *et al.* Penicillamine-induced elastosis perforans serpiginosa and cutis laxa in Wilson's disease. *Br J Dermatol* 2000; 142: 560–1.
7. Arzori L, *et al.* D-penicillamine elastosis perforans serpiginosa: description of two cases and review of the literature. *Dermatol Online J* 2011; 17: 3.
8. Sahn EE, *et al.* D-Penicillamine-induced elastosis perforans serpiginosa in a child with juvenile rheumatoid arthritis. *J Am Acad Dermatol* 1989; 20: 979–88.

LICHEN PLANUS. There have been rare reports of lichen planus in patients with primary biliary cirrhosis taking penicillamine,[1,2] although the role of penicillamine has been questioned. Oral lichen planus associated with penicillamine has also been reported[3] in patients with rheumatoid arthritis.

1. Powell FC, Rogers RS. Primary biliary cirrhosis, penicillamine, and lichen planus. *Lancet* 1981; ii: 525.
2. Powell FC, *et al.* Lichen planus, primary biliary cirrhosis and penicillamine. *Br J Dermatol* 1982; 107: 616.
3. Blasberg B, *et al.* Lichenoid lesions of the oral mucosa in rheumatoid arthritis patients treated with penicillamine. *J Rheumatol* 1984; 11: 348–51.

PEMPHIGUS. Bullous skin disorders are established adverse effects of penicillamine and appear to have an autoimmune basis.[1] Pemphigus-spectrum disorders have been most commonly reported, including pemphigus vulgaris, pemphigus foliaceus, herpetiform pemphigus, pemphigus erythematosus, benign mucous membrane pemphigoid, cicatricial pemphigoid, and combined pemphigus and pemphigoid features.

1. Bialy-Golan A, Brenner S. Penicillamine-induced bullous dermatoses. *J Am Acad Dermatol* 1996; 35: 732–42.

PSORIASIFORM ERUPTIONS. Two patients with rheumatoid arthritis developed psoriasiform eruptions during penicillamine treatment.[1] In 1 patient the eruption resolved when penicillamine was stopped but worsened when treatment was restarted.

1. Forgie JC, Highet AS. Psoriasiform eruptions associated with penicillamine. *BMJ* 1987; 294: 1101.

SCLERODERMA. Penicillamine has been used in the treatment of scleroderma and systemic sclerosis (see under Uses, p. 1567.3). However, scleroderma, with evidence of pulmonary involvement, developed in a 14-year-old boy with Wilson's disease who had been treated with penicillamine for 11 years[1] and the suitability of penicillamine for this indication has therefore been questioned.

1. Miyagawa S, *et al.* Systemic sclerosis-like lesions during long-term penicillamine therapy for Wilson's disease. *Br J Dermatol* 1987; 116: 95–100.

TOXIC EPIDERMAL NECROLYSIS. A 56-year-old woman developed agranulocytosis and toxic epidermal necrolysis 7 weeks after starting therapy with penicillamine 250 mg daily for primary biliary cirrhosis.[1] Severe toxic epidermal necrolysis has also been reported[2] in a woman taking penicillamine for Wilson's disease.

1. Ward K, Weir DG. Life threatening agranulocytosis and toxic epidermal necrolysis during low dose penicillamine therapy. *Ir J Med Sci* 1981; 150: 252–3.
2. Chan HL. Observations on drug-induced toxic epidermal necrolysis in Singapore. *J Am Acad Dermatol* 1984; 10: 973–8.

Genetic factors. There is evidence that some patients may have a genetically determined increased susceptibility to the adverse effects of penicillamine. Several studies have suggested that rheumatoid arthritis patients with a poor capacity for producing sulfoxides may be more susceptible to the toxic effects of penicillamine.[1,2] Patients with primary biliary cirrhosis also appear to have poor sulfoxidation capacity,[3] and this may contribute to their high incidence of adverse reactions to penicillamine, although no association between penicillamine toxicity and sulfoxidation status was found in a study of 20 such patients.[4]

Several studies have also suggested that certain histocompatibility antigens may increase susceptibility to penicillamine toxicity. An increased incidence of adverse reactions was noted[2] in patients with HLA-DR3, while other studies have shown associations between proteinuria and HLA antigens B8 and DR3,[5,6] myasthenia gravis and Bw35 and DR1,[7] thrombocytopenia and HLA antigens DR4,[3,6] A1,[5] and C4BQ0,[5] and polymyositis or dermatomyositis and HLA antigens B18, B35, and DR4.[8] However, not all studies have reported the same associations, and the clinical usefulness of sulfoxidation testing or HLA-typing is not established.[6,9]

1. Panayi GS, *et al.* Deficient sulphoxidation status and D-penicillamine toxicity. *Lancet* 1983; i: 414.
2. Emery P, *et al.* D-Penicillamine induced toxicity in rheumatoid arthritis: the role of sulphoxidation status and HLA-DR3. *J Rheumatol* 1984; 11: 626–32.
3. Olomu A, *et al.* Poor sulphoxidation in primary biliary cirrhosis. *Lancet* 1985; i: 1504.
4. Mitchison HC, *et al.* D-penicillamine-induced toxicity in primary biliary cirrhosis (PBC): the role of sulphoxidation status. *Gut* 1986; 27: A622.
5. Stockman A, *et al.* Genetic markers in rheumatoid arthritis: relationship to toxicity from D-penicillamine. *J Rheumatol* 1986; 13: 269–73.
6. Moens HJB, *et al.* Longterm followup of treatment with D-penicillamine for rheumatoid arthritis: effectivity and toxicity in relation to HLA antigens. *J Rheumatol* 1987; 14: 1115–19.
7. Garlepp MJ, *et al.* HLA antigens and acetylcholine receptor antibodies in penicillamine induced myasthenia gravis. *BMJ* 1983; 286: 338–40.
8. Carroll GJ, *et al.* Penicillamine induced polymyositis and dermatomyositis. *J Rheumatol* 1987; 14: 995–1001.
9. Hall CL. Penicillamine nephropathy. *BMJ* 1988; 297: 137.

Systemic lupus erythematosus. A syndrome resembling SLE developed in 6 women with long-standing severe rheumatoid arthritis while taking penicillamine;[1] this represented a frequency of penicillamine-induced lupus erythematosus of about 2%. All 6 had developed previous cutaneous reactions to gold therapy. A case of bullous SLE associated with penicillamine has also been reported.[2]

1. Chalmers A, *et al.* Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. *Ann Intern Med* 1982; 97: 659–63.
2. Condon C, *et al.* Penicillamine-induced type II bullous systemic lupus erythematosus. *Br J Dermatol* 1997; 136: 474–5.

Precautions

Penicillamine is contra-indicated in patients with lupus erythematosus or a history of penicillamine-induced agranulocytosis, aplastic anaemia, or severe thrombocytopenia. It is also contra-indicated in patients with moderate or severe renal impairment, and should be used with care in those with mild impairment; a reduced dose may be necessary. Penicillamine is a degradation product of penicillin and patients who are allergic to penicillin may show cross-sensitivity to penicillamine although this appears to be rare.

Patients need to be carefully monitored for adverse effects; elderly patients may be at increased risk of toxicity. In all patients, full blood counts and renal function should be assessed before starting treatment. During therapy full blood counts and urinalysis should be carried out periodically. Liver function tests at 6-monthly intervals have also been recommended.

Therapy should ideally be continuous for cystinuria or Wilson's disease as interruptions to treatment for even a few days have been followed by sensitivity reactions when restarting penicillamine.

Oral pyridoxine 25 mg daily may be given to patients on long-term therapy, especially if they are on a restricted diet, since penicillamine increases the requirement for this vitamin.

A reduced dose of penicillamine has been suggested for patients undergoing surgery (see Anaesthesia and Surgery, below).

Anaesthesia and surgery. Penicillamine may delay wound healing due to its effects on collagen and elastin and US licensed product information suggests that the dose should be reduced to 250 mg daily for 6 weeks before surgery and during the postoperative period until healing has taken place.

The effects of penicillamine on muscle function should also be considered in patients requiring anaesthesia; a 57-year-old woman[1] with penicillamine-induced myasthenia developed prolonged postoperative apnoea, necessitating artificial ventilation.

1. Pried MJ, Protheroe DT. D-Penicillamine induced myasthenia gravis: its relevance for the anaesthetist. *Br J Anaesth* 1986; **58**: 1191–3.

Breast feeding. Although data are scarce, a review reported no adverse effects in the infants of nursing mothers taking penicillamine for Wilson's disease; the concentration of zinc and copper in the breast milk was reduced in one study.[1]

1. Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31**: 531–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies penicillamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 05/09/11)

Pregnancy. Penicillamine teratogenicity has been reviewed.[1] Evidence of the embryotoxicity of maternal penicillamine exposure in *animal* studies had been confirmed in humans by 5 reports of cutis laxa in neonates of mothers who had taken penicillamine during pregnancy; 3 further reports of intra-uterine brain injury were less characteristic. Nevertheless most pregnancy outcomes were normal. No birth defects had been reported when penicillamine was stopped in early pregnancy. In conditions where there are safer treatment options, it is advisable to stop penicillamine during pregnancy; however, it is generally recommended that women taking penicillamine for Wilson's disease should continue throughout pregnancy since the benefits outweigh the risks. Of 153 pregnancies in 111 women with Wilson's disease treated with penicillamine, there were 144 normal neonates (1 premature), 4 elective abortions, 1 miscarriage, and 4 infants with birth defects: mannosidosis (1), cleft lip and palate (1), and transient cutis laxa (2).[2] A reduced dose of penicillamine 0.75 to 1 g daily has been used during the first 2 trimesters in women with well-controlled Wilson's disease, reducing to 500 mg daily during the last trimester. If a caesarean section is planned, the dose should be reduced as described for surgery, see above.

For a report of congenital hypothyroidism associated with use of penicillamine during pregnancy, see Effects on Endocrine Function, p. 1568.3.

1. Rosa FW. Teratogen update: penicillamine. *Teratology* 1986; **33**: 127–31.
2. Sternlieb I. Wilson's disease and pregnancy. *Hepatology* 2000; **31**: 531–2.

Interactions

Penicillamine forms chelates with metal ions and oral absorption may be reduced if it is given with iron or other metals, antacids, or food. Penicillamine should be taken on an empty stomach and it has been recommended that there should be an interval of at least 2 hours between taking penicillamine and iron supplements or antacids. Mineral supplements should be avoided. It has also been suggested that digoxin should not be given within 2 hours of penicillamine, see Interactions of Digoxin, p. 1358.1. Additive toxicity may occur if penicillamine is given with drugs that have adverse renal or haematological effects.

Antacids or food. In a single-dose study in 6 healthy subjects, penicillamine given orally immediately after food or a dose of an antacid mixture (aluminium hydroxide, magnesium hydroxide, and simeticone), resulted in plasma concentrations of penicillamine that were 52% and 66%, respectively, of those obtained in a fasting state. Results suggested that the reduction in plasma-penicillamine concentrations was associated with decreased absorption.[1] Another study[2] showed that the reduction of penicillamine plasma concentrations produced by aluminium- and magnesium-containing antacids did not occur with sodium bicarbonate, and thus the interaction was probably a result of chelation rather than a pH effect.

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulphate. *Clin Pharmacol Ther* 1983; **33**: 465–70.
2. Ilan A, Welling PG. Pharmacokinetics of oral 500 mg penicillamine: effect of antacids on absorption. *Biopharm Drug Dispos* 1986; **7**: 401–5.

Diazepam. For a report of re-activation of intravenous diazepam-induced phlebitis by oral penicillamine, see under Diazepam, p. 1070.3.

Gold. There have been conflicting reports on the effect of previous gold therapy on the subsequent development of penicillamine toxicity in patients with rheumatoid arthritis.

Some studies[1,2] have suggested that adverse effects with penicillamine may be more common in patients who have previously reacted adversely to gold, but others[3,4] have found no correlation. One study[5] found that although the overall incidence of adverse effects with penicillamine appeared unaffected by prior gold therapy, bone-marrow depression and rashes were more common in those previously given gold. It has been suggested[2] that the interaction occurs due to mobilisation of gold from the tissues by penicillamine, and an interval of at least 6 months between gold and penicillamine in patients with prior gold toxicity was recommended. However, another report[6] found that the interval between gold and penicillamine had no influence on the development of toxicity and suggested that there might be a common genetic susceptibility in certain patients. A patient who had developed myasthenia with penicillamine had a recurrence with gold therapy,[7] but another study[4] found no evidence that the adverse effects of gold were increased in those with prior penicillamine toxicity.

1. Hill H. Penicillamine and previous treatment with gold. *BMJ* 1978; **2**: 961.
2. Dodd MJ, *et al.* Adverse reactions to D-penicillamine after gold toxicity. *BMJ* 1980; **280**: 1498–1500.
3. Multi-centre Trial Group. Absence of toxic or therapeutic interaction between penicillamine and previously administered gold in a trial of penicillamine in rheumatoid disease. *Postgrad Med J* 1974; **50** (suppl 2): 77–8.
4. Steven MM, *et al.* Does the order of second-line treatment in rheumatoid arthritis matter? *BMJ* 1982; **284**: 79–81.
5. Webley M, Coomes EN. Is penicillamine therapy in rheumatoid arthritis influenced by previous treatment with gold? *BMJ* 1978; **2**: 91.
6. Smith PJ, *et al.* Influence of previous gold toxicity on subsequent development of penicillamine toxicity. *BMJ* 1982; **285**: 595–6.
7. Moore AP, *et al.* Penicillamine induced myasthenia reactivated by gold. *BMJ* 1984; **288**: 192–3.

Insulin. Unexplained hypoglycaemia in 2 patients with type 1 diabetes occurred 6 to 8 weeks after penicillamine treatment for rheumatoid arthritis was started.[1] Both patients required a reduction in their insulin dose. A possible immunological mechanism has been proposed.[1,2]

1. Elling P, Elling H. Penicillamine, captopril, and hypoglycemia. *Ann Intern Med* 1985; **103**: 644–5.
2. Becker RC, Martin RG. Penicillamine-induced insulin antibodies. *Ann Intern Med* 1986; **104**: 127–8.

Iron. Plasma-penicillamine concentrations were reduced to 35% when penicillamine was given after a dose of ferrous sulfate in healthy subjects.[1] Patients stabilised on penicillamine while on oral iron therapy were considered unlikely to respond fully to penicillamine and would be exposed to a large increase in penicillamine absorption with possible adverse reactions if the iron was stopped.[2]

1. Osman MA, *et al.* Reduction in oral penicillamine absorption by food, antacid, and ferrous sulfate. *Clin Pharmacol Ther* 1983; **33**: 465–70.
2. Harkness JAL, Blake DR. Penicillamine nephropathy and iron. *Lancet* 1982; **ii**: 1368–9.

Probenecid. Probenecid may reduce the beneficial effects of penicillamine in cystinuria, and it has been suggested[1] that hyperuricaemic cystinuric patients should not be given both drugs.

1. Yu T-F, *et al.* Studies on the metabolism of D-penicillamine and its interaction with probenecid in cystinuria and rheumatoid arthritis. *J Rheumatol* 1984; **11**: 467–70.

Pharmacokinetics

Penicillamine is rapidly but variably absorbed from the gastrointestinal tract and peak plasma concentrations occur within 1 to 3 hours. It is reported to be more than 80% bound to plasma proteins, particularly albumin. Penicillamine undergoes some metabolism in the liver, to *S*-methyl penicillamine. It is mainly excreted in the urine as disulfides, along with some *S*-methyl penicillamine and unchanged drug; a small amount may be excreted in the faeces. Elimination is biphasic with an initial elimination half-life of about 1 to 3 hours followed by a slower phase, suggesting gradual release from tissues.

Reviews.

1. Netter P, *et al.* Clinical pharmacokinetics of D-penicillamine. *Clin Pharmacokinet* 1987; **13**: 317–33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cuprimine; Cupripen; *Austral.*: D-Penamine; *Austria*: Artamin; *Braz.*: Cuprimine; *Canad.*: Cuprimine; *Cz.*: Metalcaptase; *Denm.*: Atamir; *Fr.*: Trolovol; *Ger.*: Metalcaptase; *Gr.*: Cupripen†; *India*: Artamin; Cilamin; Distamin; *Irl.*: Distamine; *Ital.*: Pemine; *Jpn*: Metalcaptase; *Malaysia*: Artamin; *Mex.*: Adalken; Sufortan; *Neth.*: Gerodyl; *NZ*: D-Penamine; *Pol.*: Cuprenil; *Port.*: Kelatine; Trolovol; *Rus.*: Cuprenil (Купренил); *S.Afr.*: Metalcaptase†; *Spain*: Cupripen; *Switz.*: Mercaptyl†; *Thal.*: Cuprimine; *UK*: Distamine; *USA*: Cuprimine; Depen.

Pharmacopoeial Preparations
BP 2014: Penicillamine Tablets;
USP 36: Penicillamine Capsules; Penicillamine Tablets.

Pentetic Acid *(BAN, USAN, rINN)*

Acide Pentétique; Ácido pentético; Acidum Penteticum; Diethylentriaminpentaessigsäure; DTPA; Pentético, ácido; Pentetinezuur; ZK-43649; Пентетовая Кислота.

Diethylenetriamine-*NNN′N″N″*-penta-acetic acid.

$C_{14}H_{23}N_3O_{10}$=393.3

CAS — 67-43-6.

UNII — 7A314HQM0I.

Pharmacopoeias. In *US*.

USP 36: (Pentetic Acid). A white odourless or almost odourless powder.

Calcium Trisodium Pentetate *(BAN, rINN)*

Ca-DTPA; Calcii Trinatrii Pentetas; Calcium Trisodium DTPA; NSC-34249; Pentetate Calcium Trisodium (USAN); Pentétate de Calcium Trisodique; Pentetato cálcico trisódico; Pentetato calcio y trisodio; Trisodium Calcium Diethylenetriaminepentaacetate; Кальция Тринатрия Пентетат.

$C_{14}H_{18}CaN_3Na_3O_{10}$=497.4

CAS — 12111-24-9.

UNII — G79YN26H5B.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (*Pentetate Sodium Calcium* for Radiopharmaceutical Preparations). A starting material for the preparation of technetium (^{99m}Tc) pentetate injection. A white or almost white, hygroscopic powder or crystals. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 8.0 to 9.5. Store in airtight containers. Protect from light.

Zinc Trisodium Pentetate *(rINNM)*

Pentétate de Zinc Trisodique; Pentetate Zinc Trisodium; Pentetato zinc y trisodio; Trisodium Zinc Diethylenetriaminepentaacetate; Zinci Trinatrii Pentetas; Zn-DTPA (zinc pentetate or zinc trisodium pentetate); Цинка Тринатрия Пентетат.

$C_{14}H_{18}N_3Na_3O_{10}Zn$=522.7

CAS — 65229-17-6 (zinc pentetate); 125833-02-5 (zinc trisodium pentetate).

UNII — NXU65IC8PG.

Uses and Administration

Pentetic acid and its salts are chelators with the general properties of the edetates (see Edetic Acid, p. 1550.3). Calcium trisodium pentetate and zinc trisodium pentetate are used in the treatment of poisoning by radioactive metals such as plutonium, americium, and curium. Calcium trisodium pentetate is more effective within the first 24 hours and is preferred for the initial dose; however, zinc depletion may occur and if further chelation is required treatment should be continued with zinc trisodium pentetate if possible.

The usual dose is 1 g of either calcium or zinc trisodium pentetate once daily, by slow intravenous injection over 3 to 4 minutes or by intravenous infusion over 30 minutes diluted in 100 to 250 mL of sodium chloride 0.9%, glucose 5%, or lactated Ringer's solution. Treatment is continued according to the estimated radioactive body burden. For patients poisoned solely by inhalation calcium trisodium pentetate or zinc trisodium pentetate may be given by nebulisation.

For doses in children, see below.

Pentetates, labelled with metallic radionuclides, are used in nuclear medicine (see Indium-111, p. 2224.3, and Technetium-99m, p. 2228.3).

Administration in children. Calcium trisodium pentetate and zinc trisodium pentetate are chelators that may be used in children for the treatment of poisoning by radioactive metals such as plutonium, americium, and curium, in the same way as for adults (see above). The usual starting and maintenance dose of either calcium or zinc trisodium pentetate is 14 mg/kg (to a maximum of 1 g) once daily, by slow intravenous injection or by intravenous infusion.

The safety and efficacy of calcium trisodium pentetate and zinc trisodium pentetate given by nebulisation has not been established for children.

Thalassaemia. Iron overload in patients with thalassaemia (p. 1124.1) is usually treated with desferrioxamine, but auditory toxicity can result. Calcium pentetic acid has been used as an alternative. A study[1] in 5 patients in whom desferrioxamine had to be withdrawn because of high-tone deafness found that the pentetate was as effective as desferrioxamine and hearing improved during treatment. Oral zinc supplements were necessary to maintain adequate plasma-zinc concentrations.

1. Wonke B, *et al.* Reversal of desferrioxamine induced auditory neurotoxicity during treatment with Ca-DTPA. *Arch Dis Child* 1989; 64: 77–82.

Adverse Effects and Precautions

Adverse effects that have been reported with calcium or zinc trisodium pentetate include headache and lightheadedness. Pentetates chelate trace metals and supplements may be needed with long-term use. Trace metals and serum-electrolytes should be monitored during use.

Other adverse effects reported with calcium trisodium pentetate include nausea and diarrhoea, injection-site reactions, chest pain, allergic reactions, dermatitis, and a metallic taste. Bronchospasm has occurred after inhalation. It should be used with caution in patients with severe haemochromatosis since fatalities have been reported when high doses were used.

Pharmacokinetics

Pentetates are rapidly distributed throughout the extracellular space and eliminated by glomerular filtration, with most of a dose excreted in the urine within 24 hours. Only a small amount (less than 3%) is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ditripentat; *Ger.*: Ditripentat-Heyl; *Israel*: DTPA: Frosstimage Kit (DTPA).

Pralidoxime (BAN, rINNM)

2-PAM; Pralidoksiimi; Pralidoksyna; Pralidossima; Pralidoxim; Pralidoxima; Pralidoximum; Пралидоксим.

2-Hydroxyiminomethyl-1-methylpyridinium.

$C_7H_9N_2O$=137.2

CAS — 6735-59-7; 495-94-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — P7MU9UTPS2.

Pralidoxime Chloride (BANM, USAN, rINNM)

2-Formyl-1-methylpyridinium Chloride Oxime; 2-PAM; 2-PAM Chloride; 2-PAMCl; Pralidoxim Chlorid; Pralidoxima, cloruro de; Pralidoxime Chlorure de; Pralidoximi Chloridum; 2-Pyridine Aldoxime Methochloride; Пралидоксима Хлорид.

$C_7H_9ClN_2O$=172.6

CAS — 51-15-0.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 38X7XS076H.

Pharmacopoeias. In *US.*

USP 36: (Pralidoxime Chloride). A white to pale yellow, odourless, crystalline powder. Freely soluble in water.

Pralidoxime Iodide (BANM, USAN, rINN)

Ioduro de pralidoxima; NSC-7760; 2-PAM Iodide; 2-PAMI; Pralidoxim Iodid; Pralidoxima, Ioduro de; Pralidoxime, Iodure de; Pralidoximi Iodidum; Yoduro de pralidoxima; Пралидоксима Йодид.

$C_7H_9IN_2O$=264.1

CAS — 94-63-3.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 7H2S4VCONT.

Pharmacopoeias. In *Chin.*

Pralidoxime Mesilate (BANM, rINNM)

Mesilato de pralidoxima; P2S; 2-PAMM; Pralidoksiimimesilaatti; Pralidoksim Mezilat; Pralidoxim Mesilat; Pralidoxima, mesilato de; Pralidoxime, Mésilate de; Pralidoxime Mesylate (USAN); Pralidoxime Methanesulphonate; Pralidoximi Mesilas; Pralidoximmesilat; Пралидоксима Мезилат.

$C_7H_9N_2O.CH_3O_3S$=232.3

CAS — 154-97-2.

ATC — V03AB04.

ATC Vet — QV03AB04.

UNII — 45CO7XIN2K

Pralidoxime Metilsulfate (BANM, rINNM)

Pralidoxima, metilsulfato de; Pralidoxime Methylsulphate; Pralidoxime, Métilsulfate de; Pralidoximi Metilsulfas; Пралидоксима Метилсульфат.

$C_7H_9N_2O.CH_3SO_4$=248.3

CAS — 1200-55-1.

ATC — V03AB04.

ATC Vet — QV03AB04.

Pharmacopoeias. In *It.*

Uses and Administration

Pralidoxime is a cholinesterase reactivator. It is used as an adjunct to, but *not* as a substitute for, atropine in the treatment of poisoning by certain cholinesterase inhibitors. Its main indication is in poisoning due to organophosphorus insecticides or related compounds (see p. 2158.3). These compounds phosphorylate and consequently inactivate cholinesterase, causing acetylcholine accumulation and muscle paralysis. Pralidoxime reactivates cholinesterase, restoring the enzymatic destruction of acetylcholine at the neuromuscular junction and relieving muscle paralysis. Use with atropine is required to counteract the adverse effects of acetylcholine accumulation, particularly at the respiratory centre. Its ability to antagonise different organophosphorus anticholinesterases varies, as reactivation is dependent on the nature of the phosphoryl group and the rate at which inhibition becomes irreversible. It is not effective in the treatment of poisoning due to phosphorus, inorganic phosphates, or organophosphates without anticholinesterase activity. Its use in the treatment of poisoning by carbamate insecticides (p. 2150.1) is controversial, see Carbamate Poisoning, below. In some countries pralidoxime is used for the treatment of overdosage by anticholinesterase drugs used to treat myasthenia gravis such as neostigmine, pyridostigmine, and ambenonium, although caution is advised when using pralidoxime in patients with myasthenia gravis, see Precautions, below.

Pralidoxime is usually given as the chloride but the mesilate, iodide, and metilsulfate salts have also been used. In severe poisoning pralidoxime is usually given as an intravenous infusion over 15 to 30 minutes, or as a slow intravenous injection over at least 5 minutes if infusion is not practicable or there is pulmonary oedema. Alternatively, for less severe toxicity or when the intravenous route is not feasible, pralidoxime can be given by intramuscular or subcutaneous injection; it has also been given orally.

In the treatment of **organophosphorus poisoning** pralidoxime should be given as soon as possible. After about 36 hours it becomes less effective since cholinesterase inactivation usually becomes irreversible after this time; however, patients with severe poisoning may occasionally respond up to 48 hours or longer after exposure, depending on the organophosphate involved. Injections of *atropine* should be given intravenously or intramuscularly and repeated as necessary until muscarinic effects disappear or signs of atropine toxicity are seen; atropinisation should then be maintained for 48 hours or more. Large amounts of atropine may be required. See under Atropine Sulfate, p. 1311.3, for details of dosages. As soon as the effects of atropine become apparent, 1 to 2 g of *pralidoxime* chloride should be given intravenously and repeated after 1 hour and then every 10 to 12 hours if necessary. Alternatively, the *BNF* recommends pralidoxime chloride in an initial dose of 30 mg/kg given by intravenous infusion or injection; the initial dose is then followed by intravenous infusion at a rate of 8 mg/kg per hour to a usual maximum dose of 12 g in 24 hours. Pralidoxime treatment is continued until the patient has not required atropine for 12 hours.

Intramuscular dosing of pralidoxime is based on the severity of poisoning; for mild symptoms a dose of pralidoxime chloride 600 mg is given by intramuscular injection, and repeated once or twice at 15 minute intervals as needed. For more severe symptoms pralidoxime chloride 1.8 g is given intramuscularly, as 3 injections of 600 mg in rapid succession. For persistent symptoms, up to 3 further doses of 600 mg at 15 minute intervals may be given as needed, starting 1 hour after the last injection. Autoinjectors for intramuscular injection are available for emergency use, and contain pralidoxime alone, pralidoxime with atropine, or pralidoxime with atropine plus avizafone. In some countries, an oral dose of pralidoxime 1 to 3 g, as the metilsulfate, is given every 5 hours for milder toxicity.

For **antimyasthenic overdose** an initial dose of pralidoxime chloride 1 to 2 g is given by intravenous infusion, followed by an intravenous infusion of 0.5 to 1 g/hour; alternatively, the initial dose can be repeated after 1 hour and then every 3 to 8 hours if needed.

The dose of pralidoxime may need to be reduced in patients with renal impairment.

Treatment may be monitored by the determination of blood-cholinesterase concentrations and clinical symptoms.

Other oximes with cholinesterase-reactivating properties that have been used similarly include asoxime chloride (p. 1541.1), obidoxime chloride (p. 1566.3), and trimedoxime bromide (p. 1579.1).

Administration in children. Pralidoxime chloride is used in children as an adjunct to atropine in the treatment of organophosphorus poisoning; the *BNFC* recommends the same dose as that recommended by the *BNF* for adults, see above.

Carbamate poisoning. The use of pralidoxime for poisoning due to carbamate insecticides is controversial. Licensed product information states that pralidoxime should not be used to treat poisoning by carbamate pesticides as it may increase toxicity, and it has been suggested that as carbamate-induced cholinesterase inhibition is spontaneously reversible, oxime therapy is not necessary. However, there are reports of successful use of pralidoxime in carbamate poisoning,[1-3] and it is suggested, with atropine, as a treatment option by some authorities.

1. Burgess JL, *et al.* Aldicarb poisoning: a case report with prolonged cholinesterase inhibition and improvement after pralidoxime therapy. *Arch Intern Med* 1994; 154: 221–4.
2. Tracqui A, *et al.* Repeated measurements of aldicarb in blood and urine in a case of nonfatal poisoning. *Hum Exp Toxicol* 2001; 20: 657–60.
3. Hoffman RS, *et al.* Use of pralidoxime without atropine in rivastigmine (carbamate) toxicity. *Hum Exp Toxicol* 2009; 28: 599–602.

Organophosphorus poisoning. Oximes such as pralidoxime are widely used in poisoning with organophosphate *pesticides*. Although benefit has been shown in *animal* studies, reviews[1,2] have pointed out that there is little good evidence from human studies to support their use and that randomised controlled studies are needed to confirm their efficacy and safety, as well as the optimum regimens to use. A randomised study[3] in patients with moderately severe poisoning with organophosphorus pesticides found that a continuous infusion of pralidoxime iodide 1 g/hour for 48 hours was more effective than a dose of 1 g every 4 hours. However, another controlled study[4] found that the WHO-recommended regimen of pralidoxime chloride 2 g as a loading dose, followed by constant infusion of 500 mg/hour, was of no benefit in patients self-poisoned with organophosphorus insecticides, despite clear evidence of reactivation of red cell acetylcholinesterase.

Cholinesterase reactivators such as the oximes have also been used for poisoning with organophosphate *nerve agents*. Studies in *animals* have suggested that the efficacy of the different oximes depends on the organophosphate involved; asoxime (p. 1541.1) and HLö-7 may be more effective than pralidoxime or obidoxime for poisoning with nerve agents, particularly for soman poisoning.[5]

1. Eyer P. The role of oximes in the management of organophosphorus pesticide poisoning. *Toxicol Rev* 2003; 22: 165–90.
2. Buckley NA, *et al.* Oximes for acute organophosphate pesticide poisoning. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2011 (accessed 01/03/11).
3. Pawar KS, *et al.* Continuous pralidoxime infusion versus repeated bolus injection to treat organophosphorus pesticide poisoning: a randomised controlled trial. *Lancet* 2006; 368: 2136–41.
4. Eddleston M, *et al.* Pralidoxime in acute organophosphorus insecticide poisoning—a randomised controlled trial. *PLoS Med* 2009; 6: e1000104. Available at: http://www.plosmedicine.org/article/fetchObjectAttachment.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1000104&representation=PDF (accessed 18/12/09)
5. Kassa J. Review of oximes in the antidotal treatment of poisoning by organophosphorus nerve agents. *J Toxicol Clin Toxicol* 2002; 40: 803–16.

Adverse Effects

Use of pralidoxime may be associated with drowsiness, dizziness, disturbances of vision, nausea, hypertension, tachycardia, headache, hyperventilation, and muscular weakness. Impaired renal function and increases in liver enzymes have been reported, as have transient increases in creatine phosphokinase. Hypertension, tachycardia, laryngospasm, and muscle rigidity have been attributed to giving pralidoxime intravenously at too rapid a rate. Large doses of pralidoxime may cause transient neuromuscular blockade.

Precautions

Pralidoxime should be used cautiously in patients with renal impairment; a reduction in dosage may be necessary. Caution is also required in giving pralidoxime to patients with myasthenia gravis as it may precipitate a myasthenic crisis. The use of pralidoxime for poisoning due to carbamate insecticides is controversial, see Carbamate Poisoning, above.

When atropine and pralidoxime are given together, the signs of atropinisation may occur earlier than might be expected when atropine is used alone.

Pregnancy. Although data are scarce, there are reports of the use of pralidoxime for poisoning in the second or third

trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Pharmacokinetics

Peak plasma concentrations of pralidoxime occur about 5 to 15 minutes after an intravenous dose. Absorption from the gastrointestinal tract is poor. It is not bound to plasma proteins and has limited distribution into the CNS. Pralidoxime is metabolised in the liver and excreted by renal tubular secretion; within 12 hours 80% of a dose is recovered unchanged in the urine, with the remainder as a metabolite. The elimination half-life is about 1 to 3 hours.

References.

1. Sidell FR, Groff WA. Intramuscular and intravenous administration of small doses of 2-pyridinium aldoxime methochloride to man. *J Pharm Sci* 1971; 60: 1224–8.
2. Siddell FR, *et al.* Pralidoxime methanesulfonate: plasma levels and pharmacokinetics after oral administration to man. *J Pharm Sci* 1972; 61: 1136–40.
3. Swartz RD, *et al.* Effects of heat and exercise on the elimination of pralidoxime in man. *Clin Pharmacol Ther* 1973; 14: 83–9.
4. Schexnayder S, *et al.* The pharmacokinetics of continuous infusion pralidoxime in children with organophosphate poisoning. *J Toxicol Clin Toxicol* 1998; 36: 549–55.
5. Abbara C, *et al.* Pharmacokinetic analysis of pralidoxime after its intramuscular injection alone or in combination with atropine-avizafone in healthy volunteers. *Br J Pharmacol* 2010; 161: 1857–67.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Contrathion; *Braz.*: Contrathion; *Fr.*: Contrathion; *Gr.*: Contrathion; *India*: Aldopam; CBC-PAM; Clopam; Lyphe; Neopam; Nispam; Pam-A Korea; *Ital.*: Contrathion; *Malaysia*: Pampara; *Singapore*: Pam-A; *Turk.*: Contrathion†; *USA*: Protopam.

Multi-ingredient Preparations. *Fr.*: Ineurope; *UK*: Nerve Agent Antidote L4A1; *USA*: DuoDote.

Pharmacopoeial Preparations

USP 36: Pralidoxime Chloride for Injection.

Protamine *(rINNM)*

Protamin; Protamina; Protaminum; Protammina; Протамин.

CAS — 9012-00-4.
ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 72G3UY6T4N.

Protamine Hydrochloride *(BANM, rINNM)*

Cloridrato de Protamina; Hidrocloruro de protamina; Protamiinihydrokloridi; Protamina, hidrocloruro de; Protamine, chlorhydrate de; Protamin-hidroklorid; Protamin-hydrochlorid; Protaminhydrochlorid; Protaminhydroklorid; Protamini Hydrochloridum; Protamino hidrochloridas; Протамина гидрохлорид.

ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 5URD19Y60H.

Protamine Sulfate *(BAN, rINN)*

Protamiinisulfaatti; Protamin Sulfat; Protamina Solfato; Protamina, sulfato de; Protamine, Sulfate de; Protamine Sulphate; Protamini Sulfas; Protamino sulfatas; Protaminsulfat; Protamin-sulfát; Protamin-szulfát; Protaminy siarczan; Solfato di Protamina; Sulfato de protamina; Протамина Сульфат.

CAS — 9009-65-8.
ATC — V03AB14.
ATC Vet — QV03AB14.
UNII — 0DE9724IHC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Protamine Sulfate). A mixture of the sulfates of basic peptides prepared from the sperm or roe of suitable species of fish, usually from the families Clupeidae or Salmonidae. A white or almost white hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Protamine Sulfate). A purified mixture of simple protein principles obtained from the sperm or testes of suitable species of fish. Store at 2 degrees to 8 degrees in airtight containers.

Uses and Administration

Protamine is a basic protein that combines with heparin to form a stable inactive complex. Protamine is used to neutralise the anticoagulant action of heparin in the treatment of haemorrhage resulting from severe heparin or low-molecular-weight heparin overdosage. It is also used to neutralise the effect of heparin given before surgery and during extracorporeal circulation as in dialysis or cardiac surgery. Protamine is usually given as the sulfate, although the hydrochloride may also be used.

Protamine sulfate is usually given by slow intravenous injection over about 10 minutes. The dose is dependent on the amount and type of heparin to be neutralised and ideally should be titrated against the coagulability of the patient's blood. Protamine has weak anticoagulating properties and if given in excess its anticoagulant action could be significant. Not more than 50 mg of protamine sulfate should be injected for any one dose; patients should be carefully monitored as further doses may be required.

For *unfractionated heparin* the Ph. Eur. 8 specifies that 1 mg of either protamine hydrochloride or protamine sulfate precipitates not less than 100 units of heparin, assayed against a specific reference batch of heparin sodium. UK licensed product information states that each mg of protamine sulfate will usually neutralise the anticoagulant effect of at least 80 international units of heparin (lung) or at least 100 international units of heparin (mucous). US licensed product information states that each mg of protamine sulfate neutralises not less than 100 USP units of heparin. As heparin is being continuously excreted the dose should be reduced if more than 15 minutes have elapsed since intravenous heparin injection: for example, if protamine sulfate is given 30 minutes after heparin the dose may be reduced to about one-half. Alternative regimens may be necessary if heparin has been given subcutaneously or by continuous intravenous infusion. To neutralise heparin given by intravenous infusion, the heparin infusion should be stopped and 25 to 50 mg protamine sulfate given by slow intravenous injection. If heparin was given subcutaneously, 1 mg of protamine sulfate should be given for each 100 units of mucous heparin, as a slow intravenous injection of protamine sulfate 25 to 50 mg with the remainder infused over 8 to 16 hours.

For *low-molecular-weight heparins*, protamine neutralises the anti-thrombin activity but only partially neutralises the anti-factor-Xa effect: 1 mg of a protamine salt is stated to inhibit the effects of about:

- 71 units of bemiparin sodium
- 80 to 120 units of certoparin sodium
- 100 units of dalteparin sodium
- 1 mg (100 units) of enoxaparin sodium
- 82 units of reviparin sodium
- 100 units of tinzaparin sodium

The dose of protamine may need to be reduced if time has elapsed since the last dose of low-molecular-weight heparin. There may be prolonged absorption from subcutaneous injection of low-molecular-weight heparins and intermittent injection or continuous infusion of protamine sulfate may be useful.

Protamine is used in some insulin preparations to prolong the effects of insulin.

Haemorrhagic disorders. Endogenous production of heparin-like substances may, rarely, be responsible for some bleeding disorders. It has been suggested that protamine could be useful as a diagnostic aid *in vitro* and could be given intravenously for transient control of bleeding in such patients.[1,2]

1. Tefferi A, *et al.* Circulating heparin-like anticoagulants: report of five consecutive cases and a review. *Am J Med* 1990; 88: 184–8.
2. Bayly PJM, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth* 1994; 73: 840–2.

Adverse Effects and Precautions

Intravenous injection of protamine, particularly if given rapidly, may cause hypotension and bradycardia. Dyspnoea, a sensation of warmth, transient flushing, nausea and vomiting, back pain, and lassitude may also occur. Anaphylactoid reactions have been reported including circulatory collapse and myocardial infarction, capillary leak, pulmonary and systemic hypertension, angioedema, and respiratory distress syndrome. Fatal anaphylaxis has occurred. Reactions are more likely after rapid injection, large doses, or repeated dosing. Patients at risk include diabetics who have received protamine-insulin preparations, those who have previously received protamine (including those who have undergone procedures such as coronary angioplasty or cardiopulmonary bypass surgery where protamine is frequently used), and those allergic to fish. Men who are infertile or who have had a vasectomy may be at increased risk since they may have antibodies to protamine. Severe left ventricular dysfunction and abnormal pulmonary haemodynamics may also be risk factors.

Protamine has an anticoagulant effect when given in the absence of heparin or at doses in excess of those required to neutralise heparin.

When repeated doses of protamine are used to neutralise large doses of heparin, rebound bleeding which responds to further doses of protamine, may occur. Clotting parameters should be closely monitored in patients receiving such prolonged therapy.

Effects on the cardiovascular system. In a review of the toxicity of protamine,[1] adverse cardiovascular responses were considered to be of 3 types: transient hypotension related to rapid drug administration, occasional anaphylactoid responses, and rarely, catastrophic pulmonary vasoconstriction. Severe adverse reactions including marked hypotension, vascular collapse, and pulmonary oedema were described in 4 patients given protamine sulfate after cardiac surgery.[2] Previous reports of similar reactions to protamine were reviewed. A total of 17 patients had immediate anaphylactic reactions; a complement-dependent IgG antibody-mediated reaction had been found in 1 patient and 3 patients tested for allergy to protamine had positive skin tests. In 15 of these 17 patients there was evidence of previous exposure to protamine. Suspected reactions to protamine occurred in a further 10 patients after cardiac surgery. However, these reactions were characterised by severe vascular damage, manifested as noncardiogenic pulmonary oedema or persistent hypotension, and onset was delayed for 30 minutes to several hours. Evidence suggested that these reactions were not antibody mediated; only 2 of 7 evaluable patients had previous exposure. All patients required aggressive therapy. A systematic review[3] noted that serious anaphylactic reactions to protamine appeared to be rare (fewer than 1% of *treated patients*) although evidence was patchy and largely anecdotal; the most common predisposing factor appeared to be treatment with protamine-containing insulin preparations.

1. Horrow JC. Protamine: a review of its toxicity. *Anesth Analg* 1985; 64: 348–61.
2. Holland CL, *et al.* Adverse reactions to protamine sulfate following cardiac surgery. *Clin Cardiol* 1984; 7: 157–62.
3. Nybo M, Madsen JS. Serious anaphylactic reactions due to protamine sulfate: a systematic literature review. *Basic Clin Pharmacol Toxicol* 2008; 103: 192–6.

Pregnancy. Although data are scarce, there are reports of the use of protamine in the second or third trimester of pregnancy, without apparent adverse effects on the neonate.[1]

1. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Denpru; *Hong Kong*: Prosulf; *India*: Neutrahep; Newtain; Prota; *Israel*: Prosulf; *UK*: Prosulf†.

Pharmacopoeial Preparations

BP 2014: Protamine Sulphate Injection;

USP 36: Protamine Sulfate for Injection; Protamine Sulfate Injection.

Prussian Blue

Albastru de Berlin; Azul da Prússia; Azul de Prusia; Berlin Blue; Berliner Blau; Berlinerblått; Blau de Prússia; Bleu de Prusse; Błękit Pruski; Blu di Prussia; CI Pigment Blue 27; Colour Index No. 77510; Ferric Ferrocyanide; Ferric Hexacyanoferrate (II); Hexacianoferrato férrico; Insoluble Prussian Blue; Karaliaučiaus Mėlis; Preussinsininen; Pruisisch Blauw; Prussian Blue Insoluble (USAN); Prøyssisk Blå; Прусская Лазурь; Прусская Синь.

$Fe_4[Fe(CN)_6]_3$=859.2

CAS — 14038-43-8 (insoluble Prussian blue); 12240-15-2 (soluble Prussian blue); 25869-00-5 (soluble Prussian blue).
ATC — V03AB31.
ATC Vet — QV03AB31.
UNII — TLE294X33A.

NOTE. Prussian blue is available in several forms and it is not always clear from the literature which form is being referred to. CI Pigment Blue 27 has been used for both insoluble ferric hexacyanoferrate (II) (Colour Index No. 77510) and the soluble potassium, sodium, or ammonium ferric hexacyanoferrate (II) salts

Profile

Prussian blue is used in the treatment of thallium poisoning (see p. 2628.3) and for known or suspected internal contamination with radiocaesium. When given orally it forms a non-absorbable complex with thallium or caesium in the gastrointestinal tract and increases their elimination from the body; it may also bind other elements and patients should be monitored for electrolyte imbalances. Prussian blue may cause constipation and a fibre-based laxative is

recommended; mannitol is also used. Prussian blue may be mixed with food or liquid when given orally, but this may result in blue discoloration of the mouth and teeth.

The usual dose of Prussian blue is 250 to 300 mg/kg daily, or about 20 g daily given in divided doses either orally or by nasogastric tube. In the USA, a lower oral dose of 3 g three times daily is recommended; in radiocaesium contamination this can be reduced to 1 or 2 g three times daily once the internal radioactivity has been substantially decreased, which may improve gastrointestinal tolerance. For thallium poisoning, treatment should continue until the urinary excretion of thallium falls to 500 micrograms or less per 24 hours, the urine or blood concentration is less than 10 micrograms/L, or no thallium can be detected in the faeces. For radiocaesium contamination, a minimum of 30 days treatment should be given. For doses in children, see Administration in Children, below.

References.
1. Thompson DF, Church CO. Prussian blue for treatment of radiocesium poisoning. *Pharmacotherapy* 2001; 21: 1364–7.
2. Hoffman RS. Thallium toxicity and the role of Prussian blue in therapy. *Toxicol Rev* 2003; 22: 29–40.
3. Thompson DF, Callen ED. Soluble or insoluble Prussian blue for radiocesium and thallium poisoning? *Ann Pharmacother* 2004; 38: 1509–14.

Administration in children. Prussian blue is used in the treatment of children with thallium poisoning or for known or suspected internal contamination with radiocaesium. The usual dose of prussian blue is 250 to 300 mg/kg daily given in divided doses either orally or by nasogastric tube. In the USA, an oral dose of 1 g three times daily is recommended for children aged 2 to 12 years of age.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Radiogardase-Cs; *Ger.*: Antidotum Thallii-Heyl; Radiogardase-Cs; *Rus.*: Ferrocin (Ферроцин); *USA*: Radiogardase.

Sevelamer *(BAN, rINN)*

Sevelameeri; Sévelamer; Sevelámero; Sevelamerum; Севеламер.

Allylamine polymer with 1-chloro-2,3-epoxypropane.

CAS — 52757-95-6.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — 941N5DUU5C.

Sevelamer Carbonate *(BANM, USAN, rINNM)*

Carbonato de sevelámero; GT-335-012; Sévélamer Carbonate; Sevelameri Carbonas; Севеламера Карбонат.

Allylamine polymer with 1-chloro-2,3-epoxypropane carbonate.

CAS — 845273-93-0.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — 9YCX42I8IU.

Sevelamer Hydrochloride *(BANM, USAN, rINNM)*

GT16-026A; Hidrocloruro de sevelámero; Sévélamer Chlorhydrate de; Sevelameri Hydrochloridum; Sevelámero, hidrocloruro de; Севеламера Гидрохлорид.

Allylamine polymer with 1-chloro-2,3-epoxypropane hydrochloride.

CAS — 182683-00-7.
ATC — V03AE02.
ATC Vet — QV03AE02.
UNII — GLS2PGI8QG.

NOTE. The name sevelamer has been used for both sevelamer and sevelamer hydrochloride.

Uses and Administration

Sevelamer is a phosphate binder used for hyperphosphataemia in patients with chronic renal failure. It is given orally as either the carbonate or the hydrochloride in patients on haemodialysis or peritoneal dialysis; sevelamer carbonate is also used in patients with chronic kidney disease and a high serum-phosphate concentration but not requiring dialysis. The initial dose is 0.8 to 1.6 g of sevelamer carbonate or sevelamer hydrochloride three times daily with each meal, depending on the severity of hyperphosphataemia. Doses should then be adjusted according to serum-phosphate concentrations; the usual maintenance dose is from 0.8 to 4 g with each meal.

References.
1. Tonelli M, *et al.* Alberta Kidney Disease Network. Systematic review of the clinical efficacy and safety of sevelamer in dialysis patients. *Nephrol Dial Transplant* 2007; 22: 2856–66.
2. Goldsmith DR, *et al.* Sevelamer hydrochloride: a review of its use for hyperphosphataemia in patients with end-stage renal disease on haemodialysis. *Drugs* 2008; 68: 85–104.
3. Raggi P, *et al.* Ten-year experience with sevelamer and calcium salts as phosphate binders. *Clin J Am Soc Nephrol* 2010; 5 (suppl 1): S31–S40.
4. Zhang Q, *et al.* Meta-analysis comparing sevelamer and calcium-based phosphate binders on cardiovascular calcification in hemodialysis patients. *Nephrom Clin Pract* 2010; 115: c259–c267.
5. Fishbane S, *et al.* A randomized, parallel, open-label study to compare once-daily sevelamer carbonate powder dosing with thrice-daily sevelamer hydrochloride tablet dosing in CKD patients on hemodialysis. *Am J Kidney Dis* 2010; 55: 307–15.
6. Barna MM, *et al.* Sevelamer carbonate. *Ann Pharmacother* 2010; 44: 127–34.
7. Assimon MM, *et al.* The effect of sevelamer hydrochloride and calcium-based phosphate binders on mortality in hemodialysis patients: a need for more research. *Consult Pharm* 2010; 25: 41–54.
8. Biggar P, Ketteler M. Sevelamer carbonate for the treatment of hyperphosphatemia in patients with kidney failure (CKD III–V). *Expert Opin Pharmacother* 2010; 11: 2739–50.

Adverse Effects and Precautions

The most common adverse effects associated with sevelamer are gastrointestinal disturbances including constipation; dysphagia and oesophageal tablet retention, intestinal obstruction and perforation, ileus, and diverticulitis have been reported. Other adverse effects include rash and pruritus.

Sevelamer is contra-indicated in patients with hypophosphataemia and in bowel obstruction. Caution is recommended in patients with gastrointestinal disorders such as dysphagia, severe motility disorders, active inflammatory bowel disease, or in those who have had major gastrointestinal surgery as there is limited experience with sevelamer in these patients. A suspension may be preferred to tablet formulations in patients with a history of swallowing disorders.

When switching from other phosphate binders to sevelamer hydrochloride, worsening of metabolic acidosis has occurred, see also below. Sevelamer hydrochloride contains about 180 mg of chloride per gram, and serum chloride may increase during treatment as chloride may be exchanged for phosphorus in the gut. Close monitoring of both chloride and bicarbonate is recommended with sevelamer hydrochloride.

Effects on acid/base balance. Sevelamer hydrochloride has been associated with metabolic acidosis as indicated by reductions in serum-bicarbonate concentrations; this does not seem to be a problem with sevelamer carbonate.[1]

1. Pai AB, Shepler BM. Comparison of sevelamer hydrochloride and sevelamer carbonate: risk of metabolic acidosis and clinical implications. *Pharmacotherapy* 2009; 29: 554–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sevelamer as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 13/10/11)

Interactions

Sevelamer has been reported to reduce the bioavailability of ciprofloxacin (see p. 265.2), ciclosporin (see p. 1955.1), mycophenolate (see p. 1965.1), tacrolimus (see p. 1973.3), and levothyroxine (p. 2342.1). It may also affect the bioavailability of other drugs and should be given at least 3 hours before or 1 hour after drugs for which a reduction in bioavailability could be clinically significant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Renagel; *Austria*: Renagel; Renvela; *Belg.*: Renagel; Renvela; *Braz.*: Renagel; *Canad.*: Renagel; *Chile*: Renvela; *Cz.*: Renagel; Renvela; *Denm.*: Renagel; Renvela; *Fin.*: Renagel†; *Fr.*: Renagel; Renvela; *Ger.*: Renagel; Renvela; *Gr.*: Renagel; Renvela; *Hong Kong*: Renagel; *Hung.*: Renagel; Renvela; *India*: Foseal; *Irl.*: Renagel; Renvela; *Israel*: Renagel; Renvela; *Ital.*: Renagel; *Jpn*: Phosblock; Renagel; *Neth.*: Renagel; Renvela; *Norw.*: Renagel; Renvela; *NZ*: Renagel; *Pol.*: Renagel; *Port.*: Renagel; Renvela; *Rus.*: Renagel (Ренагель); *S.Afr.*: Renagel; *Singapore*: Renvela; *Spain*: Renagel; Renvela; *Swed.*: Renagel; Renvela; *Switz.*: Renagel; Renvela; *Thai.*: Renvela; *Turk.*: Renagel; *UK*: Renagel; Renvela; *USA*: Renagel; Renvela.

Sodium Calcium Edetate *(BAN, rINN)*

Calcioedetato de sodio; Calcium Disodium Edathamil; Calcium Disodium Edetate; Calcium Disodium Ethylenediaminetetra-acetate; Calcium Disodium Versenate; Calcium édétate de sodium; Calcium EDTA; Disodium Calcium Tetracemate; E385; Edetan sodno-vápenatý hydrát; Edetate Calcium Disodium (USAN); Edetato cálcico disódico; Edetato de calcio y sodio; Kalcium-nátrium-edetát; Natrii Calcii Edetas; Natrii Calcii Edetas Hydricus; Natrio-kalcio edetatas; Natriumcalciumedetat; Natriumkalciumedetat; Natriumkalsiumedetaatti; Sodium, calcium, édétate de; Sodium Calciumedetate; Sodu wapnia edetynian; Sodyum Kalsiyum Edetat; Wapniowo-disodowy edetynian; Натрия Кальция Эдетат.

The calcium chelate of disodium ethylenediaminetetraacetate; Disodium[(ethylenedinitrilo)tetraacetato]calciate(2-) hydrate.

$C_{10}H_{12}CaN_2Na_2O_8.xH_2O$=374.3 (anhydrous).

CAS — 62-33-9 (anhydrous sodium calcium edetate); 7411-34-9 (sodium calcium edetate hydrate).
UNII — 25IH6R4SGF (sodium calcium edetate); 8U5D034955 (anhydrous sodium calcium edetate).

NOTE. Do not confuse with sodium edetate; see Inappropriate Administration under Sodium Edetate, p. 1551.2.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Calcium Edetate). A white or almost white, hygroscopic, powder. Freely soluble in water; practically insoluble in alcohol. A 20% solution in water has a pH of 6.5 to 8.0. Store in airtight containers. Protect from light.

USP 36: (Edetate Calcium Disodium). White, slightly hygroscopic, odourless, crystalline powder or granules. Freely soluble in water. pH of a 20% solution in water is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. See under Edetic Acid, p. 1550.3. Sodium calcium edetate solution is also incompatible with the following solutions for injection:

- amphotericin B
- glucose 10%
- hydralazine hydrochloride
- invert sugar 10% in sodium chloride 0.9%
- Ringer's solution and lactated Ringer's solution
- sodium lactate 1.9%

Uses and Administration

Sodium calcium edetate is the calcium chelate of disodium edetate and is a chelator used in the treatment of lead poisoning (p. 2542.1). It mobilises lead from bone and tissues and aids elimination from the body by forming a stable, water-soluble, lead complex which is readily excreted by the kidneys. It may be used as a diagnostic test for lead poisoning but measurement of blood-lead concentrations is generally preferred.

Sodium calcium edetate is also a chelator of other heavy-metal polyvalent ions, including chromium, and has been used in the treatment of poisoning by radioactive metals such as plutonium.

Sodium calcium edetate is also used as a pharmaceutical excipient and as a food additive.

In the treatment of lead poisoning, sodium calcium edetate may be given by intramuscular injection or by intravenous infusion. Although the intravenous route is generally preferred, intramuscular injection may be considered for patients with lead encephalopathy and cerebral oedema as rapid infusion can increase intracranial pressure. Sodium calcium edetate may initially aggravate the symptoms of lead toxicity due to mobilisation of stored lead and it has often been given with dimercaprol (p. 1549.3) in patients who are symptomatic; the first dose of dimercaprol should preferably be given at least 4 hours before the sodium calcium edetate.

For intravenous infusion, sodium calcium edetate should be diluted with glucose 5% or sodium chloride 0.9% to a concentration of not more than 3%. Alternatively, sodium calcium edetate may be given intramuscularly in equally divided doses 8 to 12 hours apart. Intramuscular injection of sodium calcium edetate is painful and lidocaine or procaine should be added to a final concentration of 0.5% to minimise pain.

In the UK, the usual dose of sodium calcium edetate for severe toxicity or encephalopathy is 80 mg/kg daily in 2 divided doses, or 75 mg/kg once daily, by intravenous infusion over at least 1 hour. In the USA and some other countries, a dose of 1 g/m² daily by intravenous infusion over 8 to 12 hours or by intramuscular injection is suggested for asymptomatic patients; a daily dose of 1.5 g/m² given intramuscularly in divided doses may be used with dimercaprol in patients with symptomatic poisoning. Treatment is given for up to 5 days, repeated if necessary usually after an interval of at least 2 days. Any further treatment with sodium calcium edetate should then not be given for at least 7 days.

As excretion is mainly renal, an adequate urinary flow must be established and maintained during treatment. For administration in renal impairment or when there is lead nephropathy, see p. 1574.1.

Administration in children. Sodium calcium edetate is used in children as a chelator in the treatment of lead

poisoning. Children absorb considerably more ingested lead than adults and are at greater risk of developing toxicity such as encephalopathy. Some recommend intramuscular injection as the preferred route (the intravenous route has been associated with fatalities in some young children); however, it is painful and others recommend the intravenous route where possible. Last available guidance from the *American Academy of Pediatrics* considered that intravenous administration was safe and more appropriate than the intramuscular route in children; slow infusion over several hours or a continuous infusion were recommended.[1] Doses are similar to those used in adults, see p. 1573.3.

1. Anonymous. Treatment guidelines for lead exposure in children. American Academy of Pediatrics Committee on Drugs. *Pediatrics* 1995; 96: 155–60. [Retired October 2007] Also available at: http://pediatrics.aappublications.org/cgi/reprint/96/1/155 (accessed 31/08/10)

Administration in renal impairment. The dose of sodium calcium edetate should be reduced in patients with mild renal impairment and it should not be used in patients with active renal disease or during periods of anuria. In adults with lead nephropathy, the following daily intravenous or intramuscular doses have been suggested, according to serum-creatinine concentrations:

- 20 to 30 micrograms/mL: 500 mg/m² daily for 5 days
- 30 to 40 micrograms/mL: 500 mg/m² every 48 hours for 3 doses
- above 40 micrograms/mL: 500 mg/m² once weekly

These regimens may be repeated at one month intervals.

Adverse Effects

Sodium calcium edetate is nephrotoxic and glycosuria, proteinuria, and microscopic haematuria may occur; renal proximal tubular necrosis has resulted in fatal nephrosis. Glomerular changes occur rarely. Nephrotoxicity appears to be dose dependent. Thrombophlebitis has followed intravenous infusion, particularly if given rapidly or if a concentrated solution is used. Pain at the intramuscular injection site has been reported. Other adverse effects that have been reported include gastrointestinal disturbances such as nausea and diarrhoea, abdominal pain, chills, fever, malaise, headache, myalgia, arthralgia, histamine-like responses such as sneezing, nasal congestion, and lachrymation, transient hypotension, cardiac rhythm irregularities, mild increases in hepatic enzyme values, tremor, numbness, tingling, cheilosis, rash, transient bone marrow depression, anaemia, and excessive thirst.

Sodium calcium edetate chelates trace metals such as zinc within the body and zinc deficiency has been reported. Displacement of calcium from sodium calcium edetate may lead to hypercalcaemia.

Effects on the kidneys. Of 130 children with lead poisoning who received chelation therapy with sodium calcium edetate (25 mg/kg intramuscularly every 12 hours) and dimercaprol (3 mg/kg intramuscularly every 4 hours) for a total of 5 days, 21 developed clinical evidence of nephrotoxicity and in 4 severe oliguric acute renal failure began 1 or 2 days after chelation therapy was discontinued.[1] Nephrotoxicity was probably attributable to the use of sodium calcium edetate.

1. Moel DI, Kumar K. Reversible nephrotic reactions to a combined 2,3-dimercapto-1-propanol and calcium disodium ethylenediaminetetraacetic acid regimen in asymptomatic children with elevated blood lead levels. *Pediatrics* 1982; 70: 259–62.

Precautions

Sodium calcium edetate should be used with caution, if at all, in patients with renal impairment (see also Administration in Renal Impairment, above). It is also not recommended in those with hepatitis. Urinalysis, serum electrolytes, and renal and hepatic function should be monitored frequently during treatment. ECG monitoring is recommended during intravenous therapy.

Sodium calcium edetate can chelate several endogenous metals, including zinc, and may increase their excretion; therapy should be intermittent to prevent severe deficiency developing and monitoring of zinc levels may be required (see below).

Sodium calcium edetate should not be given orally in the treatment of lead poisoning as it has been suggested that absorption of lead may be increased as a result.

Pregnancy. Although data are scarce, there are reports of the use of sodium calcium edetate for poisoning in the second or third trimester of pregnancy, without adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; 3: 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Trace metal depletion. Sodium calcium edetate 500 mg/m² was given by deep intramuscular injection every 12 hours for 5 days to 10 children with asymptomatic lead poisoning.[1] As well as reducing blood-lead concentrations, sodium calcium edetate also produced a marked fall in the mean plasma-zinc concentration but this rebounded rapidly after the end of treatment. Mean urinary-zinc excretion increased about seventeenfold during the first 24 hours of therapy. Sodium calcium edetate had little effect on the plasma concentrations or urinary excretion of copper. The results suggested that careful monitoring of zinc was required during treatment with sodium calcium edetate.

1. Thomas DJ, Chisolm JJ. Lead, zinc and copper decorporation during calcium disodium ethylenediamine tetraacetate treatment of lead-poisoned children. *J Pharmacol Exp Ther* 1986; 239: 829–35.

Pharmacokinetics

Sodium calcium edetate is poorly absorbed from the gastrointestinal tract. It distributes mainly to the extracellular fluid and does not penetrate cells. It is not significantly metabolised but is excreted by the kidneys. The half-life is about 20 to 60 minutes, with about 50% of a dose is excreted in the urine in 1 hour and over 95% in 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Ledclair; *India*: Ledcure; *Irl.*: Ledclair†; *Turk.*: Libenta; *UK*: Ledclair.

Multi-ingredient Preparations. *Arg.*: Calcium C.

Pharmacopoeial Preparations
BP 2014: Sodium Calcium Edetate Infusion;
USP 36: Edetate Calcium Disodium Injection.

Sodium Cellulose Phosphate

Cellulose Sodium Phosphate (USAN); Celulosa, fosfato sódico de; Целлюлозы Фосфат Натрия.
CAS — 9038-41-9; 68444-58-6.
ATC — V03AG01.
ATC Vet — QV03AG01.
UNII — E6S1NJ4Y5Q.

Pharmacopoeias. In *US*.

USP 36: (Cellulose Sodium Phosphate). It is prepared by the phosphorylation of alpha cellulose. A free-flowing, cream-coloured, odourless, powder. Insoluble in water, in dilute acids, and in most organic solvents. The pH of a filtrate of a 5% mixture in water is between 6.0 and 9.0. The inorganic bound phosphate content is not less than 31.0% and not more than 36.0%; the free phosphate content is not more than 3.5%; and the sodium content is not less than 9.5% and not more than 13.0%, all calculated on the dried basis. The calcium binding capacity, calculated on the dried basis, is not less than 1.8 mmol per g.

Profile

Sodium cellulose phosphate, the sodium salt of the phosphate ester of cellulose, is a cation-exchange resin that exchanges sodium ions for calcium and other divalent cations. When given orally, it binds calcium ions within the stomach and intestine to form a non-absorbable complex which is excreted in the faeces. Theoretically a 5-g dose will bind about 350 mg calcium. It has been used in the treatment of absorptive hypercalciuria with recurrent formation of calcium-containing renal calculi (p. 2350.3), and in hypercalcaemia associated with osteopetrosis, sarcoidosis, idiopathic hypercalcaemia of infancy, and vitamin D intoxication.

Diarrhoea and other gastrointestinal disturbances have been reported with sodium cellulose phosphate. It should not be given to patients with primary or secondary hyperparathyroidism, hypomagnesaemia, hypocalcaemia, bone disease, or enteric hyperoxaluria, and it should be used cautiously in pregnant women and children, since they have high calcium requirements. Patients should be monitored for electrolyte disturbances.

Interactions. Sodium cellulose phosphate binds with calcium and other cations. Use with calcium or magnesium salts, including cation-donating antacids or laxatives, may reduce its efficacy. Magnesium supplements are often required in patients receiving sodium cellulose phosphate but should be given at least one hour before or after any dose of the resin since the absorption of the magnesium may otherwise be impaired.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Calcibind†.

Pharmacopoeial Preparations
USP 36: Cellulose Sodium Phosphate for Oral Suspension.

Sodium Nitrite

Azotan(III) Sodu; Dusitan sodný; E250; Natrii nitris; Natrio nitritas; Natrium Nitrit; Natrium Nitrosum; Natriumnitriet; Natriumnitritti; Natriumnitrit; Nátrium-nitrit; Natriumnitritt; Nitrit de Sodi; Nitrit de Sodiu; Nitrito de Sódio; Nitrito de Sodio; Nitrito di Sodio; Nitrito sódico; Sodio Nitrito; Sodium nitrite de; Sodu azotyn; Sodyum Nitrit; Нитрит Натрия; Азотистокислый Натрий.
$NaNO_2$=68.99
CAS — 7632-00-0.
ATC — V03AB08.
ATC Vet — QV03AB08.
UNII — M0KG633D4F.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Sodium Nitrite). Hygroscopic, colourless crystals or mass, or yellowish rods. Freely soluble in water; soluble in alcohol. Store in airtight containers.

USP 36: (Sodium Nitrite). A white to slightly yellow granular powder, or white or practically white, opaque fused masses or sticks. It is deliquescent in air. Soluble 1 in 1.5 of water; sparingly soluble in alcohol. Its solutions are alkaline to litmus. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Sodium nitrite is used with sodium thiosulfate in the treatment of severe cyanide poisoning (p. 2156.2). Sodium nitrite produces methaemoglobin which preferentially combines with cyanide ions to form cyanmethaemoglobin, thereby displacing cyanide from cytochrome oxidase and restoring aerobic metabolism. As cyanide dissociates from methaemoglobin, it is converted to relatively non-toxic thiocyanate which is excreted in the urine; sodium thiosulfate is given as a sulfur donor, accelerating the conversion of cyanide to thiocyanate. Sodium nitrite may also enhance cyanide clearance by vasodilatation.

The usual dosage regimen is 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulfate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes. The methaemoglobin concentration should not be allowed to exceed 30 to 40%. If symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses. However, the *UK National Poisons Information Service* considers the risk of methaemoglobinaemia to be excessive with a second dose of sodium nitrite and recommends that only the sodium thiosulfate be repeated if necessary. In patients with anaemia, the sodium nitrite dose should be reduced according to the haemoglobin concentration.

For doses in children, see below.

Sodium nitrite has also been suggested in the treatment of hydrogen sulfide poisoning (see p. 1799.2).

Sodium nitrite is used as a rust inhibitor, for example in instrument disinfectants. It is also used as a preservative in foods such as cured meats. Potassium nitrite is also used as a food preservative.

Sodium nitrite generates nitric oxide and is being investigated for the treatment of vaso-occlusive crisis in *sickle-cell disease*, *myocardial ischaemic-reperfusion injury*, and cerebral vasospasm.

Administration in children. Sodium nitrite is used in children with sodium thiosulfate for the treatment of cyanide poisoning. The usual regimen for children from 1 month to 18 years is sodium nitrite 4 to 10 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution, maximum 10 mL) by intravenous injection over 5 to 20 minutes, followed by sodium thiosulfate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by intravenous injection over 10 minutes. US licensed product information suggests a lower dose of sodium thiosulfate 250 mg/kg (as a 25% solution), and warns that neonates and infants under 6 months of age may be particularly susceptible to methaemoglobinaemia with sodium nitrite. As in adults (see Uses, above), doses may need to be reduced in children with anaemia.

Adverse Effects and Precautions

Sodium nitrite may cause nausea and vomiting, abdominal pain, dizziness, headache, cyanosis, tachypnoea, and dyspnoea. Blurred vision, confusion, anxiety, diaphoresis, fatigue, and generalised numbness or tingling have also been reported. Vasodilatation has resulted in syncope, hypotension, and tachycardia; arrhythmias, cardiovascular collapse, coma, convulsions, and death have occurred in overdose.

Nitrites readily oxidise haemoglobin to methaemoglobin, causing methaemoglobinaemia. Methaemoglobin concentrations should be monitored and oxygen given during sodium nitrite treatment. Caution is needed when sodium nitrite is given with other drugs that may cause methaemoglobinaemia such as procaine and sodium nitroprusside, and when used in patients with, or at high risk of, methaemoglobinaemia including those with congenital methaemoglobin reductase deficiency, neonates and infants under 6 months of age, and those with pre-existing anaemia; dose reductions should be considered in anaemic patients, see Uses and Administration, p. 1574.3. Care is also required in patients with diminished oxygen or cardiovascular reserves such as those with smoke inhalation or substantial blood loss. Patients with G6PD deficiency may be at increased risk of haemolysis with sodium nitrite.

Blood pressure should be monitored when giving sodium nitrite as rapid injection can cause hypotension. It should be used cautiously with other drugs that reduce blood pressure or volume, or that cause vasodilatation, such as antihypertensives, diuretics, and phosphodiesterase type-5 inhibitors. Sodium nitrite is excreted by the kidneys and care is needed when using in patients with renal impairment.

Carcinogenicity. Sodium nitrite is a precursor for the formation of *N*-nitroso compounds such as nitrosamines, many of which are carcinogenic in *animals*. However, data in humans are limited. Occupational exposure to sodium nitrite has been associated with a higher incidence of oesophageal cancer. Sodium nitrite was used as an anticorrosive and coolant fluid in the production of screws, and workers were required to blow excess sodium nitrite solution from screws and so their faces, respiratory tract and alimentary tract were directly exposed; their hands were also soaked in sodium nitrite solution for 8 hours each day. A cohort of 160 workers were exposed for between 16 and 23 years with 21 developing cancer, including 11 cases of oesophageal cancer, in the 30 years of follow-up; there were no malignancies in a cohort of other unexposed workers from the same factory.[1]

1. Xie T-P, *et al.* Long-term exposure to sodium nitrite and risk of esophageal carcinoma: a cohort study for 30 years. *Dis Esophagus* 2011; 24: 30–2.

Methaemoglobinaemia. Severe methaemoglobinaemia has been reported after consumption of nitrite-contaminated meat,[1-3] inadvertent ingestion of sodium nitrite,[4-8] and intentional overdose.[9]

1. Walley T, Flanagan M. Nitrite-induced methaemoglobinaemia. *Postgrad Med J* 1987; 63: 643–44.
2. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; 76: 367–8.
3. Khan A, *et al.* Deadly meatballs—a near fatal case of methaemoglobinaemia. *N Z Med J* 2006; 119: U2107. Available at: http://www.nzma.org.nz/journal/119-1239/2107/content.pdf (accessed 26/01/11)
4. Finan A, *et al.* Methaemoglobinaemia associated with sodium nitrite in three siblings. *BMJ* 1998; 317: 1138–9.
5. Anonymous. Methemoglobinemia following unintentional ingestion of sodium nitrite—New York, 2002. *MMWR* 2002; 51: 639–42.
6. Chui JSW, *et al.* Nitrite-induced methaemoglobinaemia—aetiology, diagnosis and treatment. *Anaesthesia* 2005; 60: 496–500.
7. Tung S-P, *et al.* Methaemoglobinaemia secondary to the ingestion of sodium nitrite in mistake for common salt. *Resuscitation* 2006; 70: 168–9.
8. Maric P, *et al.* Methaemoglobinaemia following ingestion of a commonly available food additive. *Med J Aust* 2008; 188: 156–8.
9. Harvey M, *et al.* Fatal methaemoglobinaemia induced by self-poisoning with sodium nitrite. *Emerg Med Australas* 2010; 22: 463–5.

Treatment of Adverse Effects

When toxicity results from the ingestion of nitrites, treatment is supportive and symptomatic; oxygen and methylthioninium chloride may be required for methaemoglobinaemia although methylthioninium chloride should not be given if cyanide poisoning is suspected since cyanide may be displaced. Exchange transfusion may be considered for severe or refractory methaemoglobinaemia.

Pharmacokinetics

Sodium nitrite is rapidly absorbed after oral dosing. In the blood nitrite reacts with haemoglobin, producing methaemoglobin; the peak effect is seen about 30 to 70 minutes after an intravenous dose. About 40% of a dose of sodium nitrite is excreted unchanged in the urine, with the remaining 60% metabolised to ammonia and similar small molecules. Elimination half-life ranges from 21 minutes (intravenous dosing) to 35 minutes (oral ingestion).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Cyanide Antidote Package; *Ital.*: Citrosil Alcolico Azzuro; *S.Afr.*: Tripac-Cyano; *USA*: Cyanide Antidote Package; Nithiodote.

Pharmacopoeial Preparations
USP 36: Sodium Nitrite Injection.

Sodium Polystyrene Sulfonate

Natrii polystyrenesulfonas; Natrii Polystyrensulfonas; Natrio polistirensulfonatas; Natriumpolystyreenisulfonaatti; Natriumpolystyrensulfonat; Natrium-polystyrensulfonat; Natriumpolystyrolsulfonat; Poliestirenosulfonato sódico; Polystyrène sulfonate sodique; Sodium Polystyrene Sulphonate; Sulfonato sódico de poliestireno; Полистирен Сульфонат Натрия.

CAS — 9003-59-2; 9080-79-9; 25704-18-1.
ATC — V03AE01.
ATC Vet — QV03AE01.
UNII — 1699G8679Z.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Sodium Polystyrene Sulfonate). An almost white to light brown powder. It contains 9.4 to 11.0% of sodium, calculated with reference to the dried substance. Each g exchanges 2.8 mmol to 3.4 mmol of potassium, calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

USP 36: (Sodium Polystyrene Sulfonate). A golden brown, fine, odourless powder containing not more than 10% of water. The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis. Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis. Insoluble in water.

Uses and Administration

Sodium polystyrene sulfonate, the sodium salt of sulfonated styrene copolymer with divinylbenzene, is a cation-exchange resin that exchanges sodium ions for potassium ions and other cations in the gastrointestinal tract when given orally or rectally. The exchanged resin is then excreted in the faeces. Each gram of resin exchanges about 3 mmol of potassium *in vitro*, and about 1 mmol *in vivo*.

Sodium polystyrene sulfonate is used to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria, and in dialysis patients (caution is required due to the sodium content). An effect may not be evident for several hours or longer, and in severe hyperkalaemia, where a rapid effect is required, other measures must also be considered (see p. 1777.1).

Serum-electrolyte concentrations should be monitored throughout treatment and doses given according to response.

The usual oral dose is 15 g up to four times daily as a suspension in water or syrup or as a sweetened paste. It should not be given in fruit juices that have a high potassium content.

When oral use is difficult, sodium polystyrene sulfonate may be given rectally as an enema. The usual daily dose is 30 g given as a suspension in 150 mL of water or glucose 10%. The enema should be retained, if possible, for at least 9 hours; higher doses, shorter retention times, and alternative vehicles have also been used. After retention of the enema the colon should be irrigated to remove the resin. Initial therapy may involve both oral and rectal routes.

For doses in children, see below.

Other polystyrene sulfonate resins include calcium polystyrene sulfonate (p. 1541.2), which is used similarly to the sodium resin and potassium polystyrene sulfonate, which has been used in the treatment of hypercalciuria. Aluminium polystyrene sulfonate, ammonium polystyrene sulfonate, and magnesium polystyrene sulfonate have all occasionally been used.

Administration in children. Sodium polystyrene sulfonate is used in neonates and children to enhance potassium excretion in the treatment of hyperkalaemia, including that associated with anuria or severe oliguria, and in dialysis patients. It may be given orally as a suspension or paste (see above), or rectally. Each 1 g of sodium polystyrene sulfonate to be given rectally is mixed with 5 to 10 mL of a methylcellulose solution; 5 mL water or glucose 10% may also be used but retention is more difficult. With rectal use the enema should be retained as long as possible and the colon then irrigated to remove the resin. Care is needed with rectal use in children as excessive dosage or inadequate dilution can result in impaction of the resin; however, the oral route is not recommended in neonates.

UK licensed product information recommends a dose of 1 g/kg daily in divided doses, reduced to a maintenance dose of 500 mg/kg daily in divided doses. Alternatively, the *BNFC* suggests doses of 125 to 250 mg/kg three or four times daily; the maximum single dose via the oral route is 15 g. In the USA, licensed product information suggests 1 g of sodium polystyrene sulfonate for each mmol of potassium.

Adverse Effects and Treatment

Gastric irritation, anorexia, nausea, vomiting, constipation, and occasionally diarrhoea may develop during treatment with sodium polystyrene sulfonate. Constipation may be severe; large doses in elderly patients, and rectal use, particularly in children, may result in faecal impaction. Gastrointestinal concretions have occurred after oral use. Intestinal necrosis, which may be fatal, and other serious gastrointestinal effects including bleeding, ulceration, ischaemic colitis, and perforation have also occurred. If constipation develops, sodium polystyrene sulfonate treatment should be stopped until normal bowel function returns (see also Precautions, below).

Serious potassium deficiency can occur with sodium polystyrene sulfonate and signs of severe hypokalaemia may include irritability, confusion, ECG abnormalities, cardiac arrhythmias, and severe muscle weakness. Like other cation-exchange resins, sodium polystyrene sulfonate is not totally selective and its use may result in other electrolyte disturbances such as hypocalcaemia and hypomagnesaemia. Significant sodium retention may also occur.

Effects on the gastrointestinal tract. Colonic necrosis, including some fatalities, has been reported[1-3] after use of enemas containing sodium polystyrene sulfonate in sorbitol. Studies in *animals*[1] suggested that the use of sorbitol was a contributory factor, although failure to irrigate the colon adequately, as recommended by the manufacturer, was also suggested[4,7] as a possible cause. Both colonic[4,7] and upper gastrointestinal necrosis[4] have also been reported after oral or nasogastric sodium polystyrene sulfonate with sorbitol, and there have also been reports of colonic necrosis with oral[9] or rectal[10] sodium polystyrene sulfonate alone.

1. Lillemoe KD, *et al.* Intestinal necrosis due to sodium polystyrene (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; 101: 267–72.
2. Wootton FT, *et al.* Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med* 1989; 111: 947–9.
3. Rogers PB, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (Kayexalate) enemas in a critically ill patient: case report and review of the literature. *J Trauma* 2001; 51: 395–7.
4. Burnett RJ. Sodium polystyrene-sorbitol enemas. *Ann Intern Med* 1990; 112: 311–12.
5. Shepard KV. Cleansing enemas after sodium polystyrene sulfonate enemas. *Ann Intern Med* 1990; 112: 711.
6. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol* 1997; 21: 60–9.
7. McGowan CE, *et al.* Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol. *South Med J* 2009; 102: 493–7.
8. Abraham SC, *et al.* Upper gastrointestinal tract injury in patients receiving kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic, and histopathologic findings. *Am J Surg Pathol* 2001; 25: 637–44.
9. Cheng BS, *et al.* Colonic necrosis and perforation following oral sodium polystyrene sulfonate (Resonium A/Kayexelate) in a burn patient. *Burns* 2002; 28: 189–90.
10. Rugolotto S, *et al.* Necrotizing enterocolitis in a 850 gram infant receiving sorbitol-free sodium polystyrene sulfonate (Kayexalate): clinical and histopathologic findings. *J Perinatol* 2007; 27: 247–9.

Effects on the lungs. Particles of sodium polystyrene sulfonate were found at autopsy in the lungs of 3 patients who had taken the resin orally and were associated with acute bronchitis and bronchopneumonia in 2 and with early bronchitis in the third.[1] It was suggested that, where possible, it may be preferable to give sodium polystyrene sulfonate rectally, but if it has to be given orally the patient should be positioned carefully to avoid aspiration.

1. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; 142: 379–81.

Precautions

Sodium polystyrene sulfonate should not be given orally to neonates, and is contra-indicated by any route in those with reduced gut motility or obstructive bowel disease. Care is also needed with rectal use in neonates and children in order to avoid impaction of the resin. Treatment should be stopped if clinically significant constipation develops. Although sorbitol has been recommended for the prophylaxis and treatment of constipation, there have been reports of colonic necrosis, including fatalities, in patients given this combination (see Effects on the Gastrointestinal Tract, above) and most licensed product information advises against the use of sorbitol with polystyrene sulfonates. Magnesium-containing laxatives are also contra-indicated (see Interactions, p. 1576.1).

Patients receiving sodium polystyrene sulfonate should be monitored for electrolyte disturbances, especially hypokalaemia. Since serum concentrations may not always reflect intracellular potassium deficiency, symptoms of hypokalaemia should also be watched for and the decision to stop treatment assessed individually.

Use of sodium polystyrene sulfonate can result in sodium overloading and it should be used cautiously in patients with renal failure or conditions requiring a restricted sodium intake, such as heart failure and severe hyper-

tension; calcium polystyrene sulfonate (p. 1541.2) may be preferred in these patients.

After use of sodium polystyrene sulfonate retention enemas, the colon should be irrigated to ensure removal of the resin.

Interactions

Sodium polystyrene sulfonate is not totally selective for potassium and may also bind other cations. When given orally with cation-donating antacids and laxatives such as magnesium hydroxide, aluminium hydroxide, or calcium carbonate, competition for binding sites may reduce the potassium-lowering effect of the resin. In addition, metabolic alkalosis may develop due to binding of the cation by the resin preventing neutralisation of bicarbonate ions in the small intestine. Seizures have been reported due to metabolic alkalosis in a patient with chronic hypocalcaemia of renal failure given magnesium hydroxide with sodium polystyrene sulfonate and use of magnesium-containing laxatives should therefore be avoided.

Ion-exchange resins may also bind other drugs, reducing their absorption. Drugs that have been affected include levothyroxine (see p. 2342.1) and lithium salts.

Hypokalaemia may exacerbate the adverse effects of digoxin and sodium polystyrene sulfonate should be used with caution in patients receiving cardiac glycosides.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Resonium A; ***Austria***: Resonium A; ***Belg.***: Kayexalate; ***Canad.***: K-Exit; Kayexalate; ***Denm.***: Resonium; ***Fin.***: Resonium; ***Fr.***: Kayexalate; ***Ger.***: Anti-Kalium Na; Elutit-Natrium; Resonium A; ***Gr.***: Kayexalate; ***Hong Kong***: Resonium A; ***Hung.***: Resonium A; ***Israel***: Kayexalate; ***Ital.***: Kayexalate; ***Neth.***: Resonium A; ***NZ***: Resonium A; ***Pol.***: Resonium A; ***Port.***: Resonium; ***S.Afr.***: Kexelate; ***Singapore***: Resinsodio; ***Spain***: Resinsodio; ***Swed.***: Resonium; ***Switz.***: Resonium A; ***Thai.***: Kayexalate; Resinsodio†; Resonium A; ***UK***: Resonium A; ***USA***: Kayexalate; Kionex; SPS; ***Venez.***: Kayexalate.

Pharmacopoeial Preparations
USP 36: Sodium Polystyrene Sulfonate Suspension.

Sodium Thiosulfate

Disodium Thiosulfate Pentahydrate; Hiposulfito sódico; Natrii thiosulfas; Natril Thiosulfas Pentahydricus; Nātrija Tiosulfāts; Natrio tiosulfatas; Natrium Thiosulfuricum; Natriumthiosulfaat; Natriumthiosulfat; Natriumtiosulfaatti; Natriumtiosulfat; Nátrium-tioszulfát; Sodium Hyposulphite; Sodium, thiosulfate de; Sodium Thiosulphate; Sodu tiosiarczan; Sodyum Tiyosülfat; Thiosíran Sodný; Thiosíran sodný pentahydrát; Tiosiarczan Sodu; Tiosíran Sodný; Tiosolfato di Sodio; Tiossulfato de Sódio; Tiosulfat de Sodi; Tiosulfat de Sodiu; Tiosulfato sódico; Тиосульфат Натрия.

$Na_2S_2O_3.5H_2O$=248.2

CAS — 7772-98-7 (anhydrous sodium thiosulfate); 10102-17-7 (sodium thiosulfate pentahydrate).

ATC — V03AB06.

ATC Vet — QV03AB06.

UNII — HX1032V43M (sodium thiosulfate); L0IYT1O31N (anhydrous sodium thiosulfate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Thiosulfate). Colourless transparent crystals; efflorescent in dry air. It dissolves in its own water of crystallisation at about 49 degrees. Very soluble in water; practically insoluble in alcohol. A 10% solution in water has a pH of 6.0 to 8.4. Store in airtight containers.

USP 36: (Sodium Thiosulfate). Large, colourless crystals, or a coarse, crystalline powder. Is deliquescent in moist air and effloresces in dry air at temperatures exceeding 33 degrees. Soluble 1 in 0.5 of water; insoluble in alcohol. Its solutions are neutral or faintly alkaline to litmus. Store in airtight containers.

Incompatibility. Sodium thiosulfate may reduce the activity of some preservatives, including bronopol (p. 1740.3), phenylmercuric salts (see Phenylmercuric Nitrate, p. 1765.2), and thiomersal (p. 1771.3).

Stability. Solutions of sodium thiosulfate 50% stored in air developed cloudiness or a deposit after autoclaving.[1] Addition of sodium phosphate 0.5% or 1.2% improved stability but solutions became cloudy or developed a deposit after 12 and 6 weeks respectively at 25 degrees. Solutions containing sodium bicarbonate 0.5% became cloudy or developed a deposit after 12 weeks at 25 degrees. No significant improvement in stability was obtained when the concentration of sodium thiosulfate was reduced to 30% or 15%, or when the injection was sealed under nitrogen.

1. Anonymous. Sodium thiosulphate injection—effect of additives on stability. *PSGB Lab Rep* P/75/3 1975.

Uses and Administration

Sodium thiosulfate is used in the treatment of cyanide poisoning (p. 2156.2). Sodium thiosulfate may be effective alone in less severe cases of cyanide poisoning or in acrylonitrile poisoning, but it is often used with sodium nitrite (p. 1574.3). Sodium thiosulfate has also been used to prevent cyanide poisoning induced by sodium nitroprusside.

Sodium thiosulfate acts as a sulfur donor for the enzyme rhodanese, which catalyses the conversion of cyanide to relatively non-toxic thiocyanate, and thus accelerates the detoxification of cyanide.

The usual dosage regimen is 300 mg of sodium nitrite (10 mL of a 3% solution) given intravenously over 2 to 20 minutes followed by 12.5 g of sodium thiosulfate (50 mL of a 25% solution or 25 mL of a 50% solution) given intravenously over 10 minutes. If symptoms of cyanide toxicity recur, it has been suggested that the injections of nitrite and thiosulfate may be repeated after 30 minutes at half the initial doses. However, the *UK National Poisons Information Service* only recommends a further dose of sodium thiosulfate if necessary, since it considers the risk of methaemoglobinaemia to be excessive with a second dose of sodium nitrite. For doses in children, see below.

Sodium thiosulfate is used as an isotonic 4% solution in the management of extravasation of chlormethine and has been tried in the management of extravasation of some other antineoplastics (but see below).

Sodium thiosulfate has been used for its antifungal properties. Sodium thiosulfate and magnesium thiosulfate are included in mixed preparations for a variety of disorders.

Administration in children. Sodium thiosulfate is used in children in the treatment of cyanide poisoning. It may be effective alone in less severe cases of cyanide poisoning or in acrylonitrile poisoning, but it is often used with sodium nitrite. The usual regimen for children from 1 month to 18 years is sodium nitrite 4 to 10 mg/kg to a maximum of 300 mg (0.13 to 0.33 mL/kg of a 3% solution, maximum 10 mL) by intravenous injection over 5 to 20 minutes, followed by sodium thiosulfate 400 mg/kg to a maximum of 12.5 g (as a 25 or 50% solution) by intravenous injection over 10 minutes. However, US licensed product information suggests a lower dose of sodium thiosulfate 250 mg/kg (as a 25% solution).

Antineoplastic toxicity. Sodium thiosulfate may be used in the management of extravasation of chlormethine and some other antineoplastics (although this is a contentious area, see p. 731.3). It is also used to inactivate some antineoplastics before disposal.

Sodium thiosulfate, given by intravenous infusion, has also been investigated for reducing the systemic toxicity of some antineoplastics. It has been reported to reduce the incidence of nephrotoxicity associated with intraperitoneal cisplatin (see Prophylaxis under Effects on the Kidneys, p. 767.3) and to reduce hearing loss associated with carboplatin (see Effects on the Ears, p. 760.1).

Bromate poisoning. Sodium thiosulfate has been used in the treatment of bromate poisoning[1,2] although its clinical efficacy is unclear;[3] it is thought to act by reducing bromate to the less toxic bromide ion, but evidence is lacking.[3,4] Although it has been given orally, this is no longer recommended since toxic sulfide may be formed.[4] However, intravenous sodium thiosulfate may have a role in some clinical circumstances.[4,5]

1. Lue JN, *et al.* Bromate poisoning from ingestion of professional hair-care neutralizer. *Clin Pharm* 1988; 7: 66–70.
2. Lichtenberg R, *et al.* Bromate poisoning. *J Pediatr* 1989; 114: 891–4.
3. McElwee NE, Kearney TE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 570, 572.
4. De Vriese A, *et al.* Severe acute renal failure due to bromate intoxication: report of a case and discussion of management guidelines based on a review of the literature. *Nephrol Dial Transplant* 1997; 12: 204–9.
5. Johnson CE. Sodium thiosulfate unproven as bromate antidote. *Clin Pharm* 1988; 7: 572.

Calciphylaxis. Sodium thiosulfate has been used successfully to treat patients with calcification of skin, soft-tissues, and arterioles (calcific uraemic arteriolopathy). However, controlled studies are lacking.

References.
1. Hayden MR, *et al.* Vascular ossification-calcification in metabolic syndrome, type 2 diabetes mellitus, chronic kidney disease, and calciphylaxis-calcific uremic arteriolopathy: the emerging role of sodium thiosulfate. *Cardiovasc Diabetol* 2005; 4: 4. Available at: http://www.cardiab.com/content/pdf/1475-2840-4-4.pdf (accessed 22/12/09)
2. Brucculeri M, *et al.* Long-term intravenous sodium thiosulfate in the treatment of a patient with calciphylaxis. *Semin Dial* 2005; 18: 431–4.
3. Araya CE, *et al.* Sodium thiosulfate treatment for calcific uremic arteriolopathy in children and young adults. *Clin J Am Soc Nephrol* 2006; 1: 1161–6.
4. Baker BL, *et al.* Calciphylaxis responding to sodium thiosulfate therapy. *Arch Dermatol* 2007; 143: 269–70.
5. Ackermann F, *et al.* Sodium thiosulfate as first-line treatment for calciphylaxis. *Arch Dermatol* 2007; 143: 1336–7.
6. Subramaniam K, *et al.* Complete resolution of recurrent calciphylaxis with long-term intravenous sodium thiosulfate. *Australas J Dermatol* 2008; 49: 30–4.
7. Hayden MR, *et al.* Calciphylaxis: calcific uremic arteriolopathy and the emerging role of sodium thiosulfate. *Int Urol Nephrol* 2008; 40: 443–51.
8. Musso CG, *et al.* Oral sodium thiosulfate solution as a secondary preventive treatment for calciphylaxis in dialysis patients. *Saudi J Kidney Dis Transpl* 2008; 19: 820–1.
9. Hackett BC, *et al.* Calciphylaxis in a patient with normal renal function: response to treatment with sodium thiosulfate. *Clin Exp Dermatol* 2009; 34: 39–42.
10. Kalisiak M, *et al.* Calcific uremic arteriolopathy (calciphylaxis): successful treatment with sodium thiosulfate in spite of elevated serum phosphate. *J Cutan Med Surg* 2009; 13 (suppl 1): S29–34.
11. Schlieper G, *et al.* Sodium thiosulfate in the treatment of calcific uremic arteriolopathy. *Nat Rev Nephrol* 2009; 5: 539–43.
12. Musso CG, *et al.* Use of sodium thiosulfate in the treatment of calciphylaxis. *Saudi J Kidney Dis Transpl* 2009; 20: 1065–8.
13. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. *Semin Dial* 2010; 23: 258–62.
14. Micelli S, *et al.* Sodium thiosulfate not always resolves calciphylaxis: an ambiguous response. *Ren Fail* 2011; 33: 84–7.

Adverse Effects and Precautions

The toxicity of sodium thiosulfate is low. Hypernatraemia, hypotension, nausea and vomiting, diarrhoea, diuresis, and metabolic acidosis have been reported and are thought to be due to both the intrinsic osmotic properties of sodium thiosulfate, and from thiocyanate which is formed when sodium thiosulfate is used to treat cyanide poisoning. An increased clotting time has occurred 1 to 3 days after use of sodium thiosulfate. A salty taste in the mouth and a warm sensation over the body have also been reported.

Sodium thiosulfate may exacerbate hypertension or oedema and should be used with caution in patients who may have these symptoms such as those with congestive heart failure, liver cirrhosis, renal impairment, and toxaemia of pregnancy.

For other adverse effects associated with the production of thiocyanate, see Adverse Effects, under Sodium Nitroprusside, p. 1497.3.

Pharmacokinetics

Sodium thiosulfate is poorly absorbed from the gastrointestinal tract. After intravenous injection it is distributed throughout the extracellular fluid, and the thiosulfate is oxidised to sulfate or incorporated into endogenous sulfur compounds. Sodium thiosulfate is excreted in the urine with the reported elimination half-life ranging from about 20 minutes to 3 hours.

An intravenous infusion of sodium thiosulfate 12 g/m² was given over 6 hours to 8 patients receiving intraperitoneal antineoplastic therapy.[1] The thiosulfate was rapidly eliminated, 95% being excreted within 4 hours of stopping the infusion; on average only 28.5% of the dose was recovered unchanged in the urine. The mean plasma elimination half-life was 80 minutes.

1. Shea M, *et al.* Kinetics of sodium thiosulfate: a cisplatin neutralizer. *Clin Pharmacol Ther* 1984; 35: 419–25.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Azufracid; ***Austria***: Schwefelbad Dr Klopfer; ***Canad.***: Adasept; ***Cz.***: Carbotox; ***Fr.***: Desintex Infantile†; Desintex-Choline†; Desintex; Rhino-Sulfuryl; Vagostabyl; ***Ger.***: Lento Nit K; Schwefelbad Dr Klopfer†; ***Gr.***: Cyanide Antidote Package; Efalan; ***Hung.***: Schwefelbad Dr Klopfer†; ***India***: Histaglobulin; ***Ital.***: Antimicotica Solforata†; ***S.Afr.***: Tripac-Cyano; ***USA***: Cyanide Antidote Package; Nithiodote; Tinver; Versiclear.

Pharmacopoeial Preparations
BP 2014: Sodium Thiosulphate Injection;
USP 36: Sodium Thiosulfate Injection.

Succimer *(BAN, USAN, rINN)*

Acide Dimercaptosuccinique; Ácido dimercaptosuccínico; Dimercaptobernsteinsäure; Dimerkaptoravsyre; DIM-SA; DMSA; Kwas Dimerkaptobursztynowy; Succimère; Succimero; Succímero; Succimerum; Suksimeeri; Сукцимер.

meso-2,3-Dimercaptosuccinic acid; (*R**,*S**)-2,3-Dimercaptobutanedioic acid.

$C_4H_6O_4S_2$=182.2

CAS — 304-55-2.

UNII — DX1U2629QE.

Pharmacopoeias. In *Chin.*

Uses and Administration

Succimer is a chelator structurally related to dimercaprol (p. 1549.3). It forms water-soluble chelates with heavy metals and is used in the treatment of lead poisoning (see

p. 1577.1). It has also been used in the treatment of poisoning with other heavy metals such as mercury.

Succimer, labelled with a radionuclide such as technetium-99m (p. 2228.1), is used in nuclear medicine.

In the treatment of lead poisoning, succimer is given orally in a dose of 10 mg/kg or 350 mg/m² every 8 hours for 5 days then every 12 hours for an additional 14 days. The course of treatment may be repeated if necessary, usually after an interval of not less than 2 weeks unless blood-lead concentrations indicate the need for more prompt treatment. For further information on use in children, see below.

Administration in children. Succimer is used in children for the treatment of lead poisoning, see below. It is given orally in the same doses as those used in adults, see p. 1576.3. For young children, succimer capsules can be opened and the succimer beads taken from a spoon or sprinkled on a small amount of soft food and swallowed.

Lead poisoning. Succimer is an effective lead chelator[1,2] and is used in the management of lead poisoning (p. 2542.1). Succimer is also used in children with chronic lead exposure, and various dosage regimens have been studied.[3] It has also been used to lower lead concentrations in neonates with congenital exposure.[4,5]

Treatment is generally only indicated if blood-lead concentrations are greater than 45 micrograms per 100 mL;[6] although short-term studies[7] in children with lower concentrations have shown effective reduction of blood lead, no effect on neurodevelopmental outcome has been shown in follow-up studies[8,9] and treatment of such children remains controversial.

1. Mann KV, Travers JD. Succimer, an oral lead chelator. *Clin Pharm* 1991; 10: 914–22.
2. Bradberry S, Vale A. Dimercaptosuccinic acid (succimer; DMSA) in inorganic lead poisoning. *Clin Toxicol* 2009; 47: 617–31.
3. Farrar HC, *et al.* A comparison of two dosing regimens of succimer in children with chronic lead poisoning. *J Clin Pharmacol* 1999; 39: 180–3.
4. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; 3: 37–9.
5. Powell ST, *et al.* Succimer therapy for congenital lead poisoning from maternal petrol sniffing. *Med J Aust* 2006; 184: 84–5.
6. American Academy of Pediatrics Committee on Environmental Health. Lead exposure in children: prevention, detection, and management. *Pediatrics* 2005; 116: 1036–46. [Re-affirmed Nov 2008] Also available at: http://pediatrics.aappublications.org/cgi/reprint/116/4/1036.pdf (accessed 11/10/05)
7. Besunder JB, *et al.* Short-term efficacy of oral dimercaptosuccinic acid in children with low to moderate lead intoxication. *Pediatrics* 1995; 96: 683–7.
8. Rogan WJ, *et al.* The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med* 2001; 344: 1421–6.
9. Dietrich KN, *et al.* Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. *Pediatrics* 2004; 114: 19–26.

Mercury poisoning. Succimer, given orally, increases the renal excretion of mercury and may be used in mercury poisoning (p. 2556.3). In patients with renal impairment, the succimer-mercury chelate may accumulate, and alternative methods have been tried. Extracorporeal infusion of succimer into the arterial blood line during haemodialysis, a procedure known as extracorporeal regional complexing haemodialysis, produced a substantial clearance of mercury in an anuric patient following intoxication with inorganic mercury.[1] Clearance was about ten times greater than that achieved with haemodialysis after intramuscular dimercaprol.

A study[2] using blood samples from children being treated for lead exposure suggested that succimer had limited efficacy against low-level organic mercury exposure.

1. Kostyniak PJ, *et al.* Extracorporeal regional complexing haemodialysis treatment of acute inorganic mercury intoxication. *Hum Toxicol* 1990; 9: 137–41.
2. Cao Y, *et al.* Efficacy of succimer chelation of mercury at background exposures in toddlers: a randomized trial. *J Pediatr* 2011; 158: 480.e1–485.e1.

Adverse Effects and Precautions

The most commonly reported adverse effects with succimer are gastrointestinal disorders and increases in serum transaminases; flu-like symptoms, drowsiness, and dizziness have also occurred. Mild to moderate neutropenia has been reported in some patients and regular full blood counts are recommended; treatment should be stopped or withheld if severe neutropenia occurs. Rash may also require succimer to be stopped; rechallenge may be considered if continued treatment is necessary. Other adverse effects include headache, a metallic taste, sensorimotor neuropathy, musculoskeletal pain, arrhythmias, proteinuria, rhinitis, and cough. An allergic mucocutaneous reaction has occurred rarely.

Succimer should be used with caution in patients with renal impairment or a history of hepatic disease. Liver function should be measured before starting and at least every week during treatment.

G6PD deficiency. Haemolysis followed use of succimer in one patient with G6PD deficiency, although lead poisoning may have contributed to the reaction. Additionally, succimer did not provoke haemolysis in two G6PD-deficient children. A review concluded that although data were scarce, succimer could probably be given safely to G6PD-deficient patients.[1]

1. Youngster I, *et al.* Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Safety* 2010; 33: 713–26.

Pregnancy. Although data are scarce, there are reports of the use of succimer for poisoning in the second or third trimester of pregnancy, without adverse effects on the neonate.[1,2]

1. Shannon M. Severe lead poisoning in pregnancy. *Ambul Pediatr* 2003; 3: 37–9.
2. Bailey B. Are there teratogenic risks associated with antidotes used in the acute management of poisoned pregnant women? *Birth Defects Res A Clin Mol Teratol* 2003; 67: 133–40.

Pharmacokinetics

Succimer is rapidly but variably absorbed after oral doses. It undergoes rapid and extensive metabolism and is excreted mainly in the urine as metabolites. The succimer-lead chelate is eliminated in the urine and the bile, and undergoes enterohepatic recycling.

References.

1. Dart RC, *et al.* Pharmacokinetics of meso-2,3-dimercaptosuccinic acid in patients with lead poisoning and in healthy adults. *J Pediatr* 1994; 125: 309–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.:* Succicaptal; *Gr.:* Succicaptal; *USA:* Chemet.

Sucroferric Oxyhydroxide *(USAN)*

PA-21.

Polynuclear iron(III) oxyhydroxide stabilised with sucrose and starches.

$FeHO_2.xC_{12}H_{22}O_{11}.y\ (C_6H_{10}O_5)_n$

CAS — 12134-57-5.

ATC — V03AE05.

Profile

Sucroferric oxyhydroxide is a polynuclear iron (III)-oxyhydroxide stabilised with sucrose and starches. It is used as a phosphate binder for hyperphosphataemia in patients with chronic renal failure requiring haemodialysis. Doses are usually expressed in terms of the iron content; each tablet contains 500 mg of iron, equivalent to about 2.5 g of sucroferric oxyhydroxide. It is given orally in a usual initial dose of one tablet 3 times daily with meals, and then adjusted according to serum-phosphate concentrations in steps of one tablet daily at weekly intervals. The usual daily dose is 3 or 4 tablets. Gastrointestinal adverse effects have occurred, consistent with those commonly seen with oral iron preparations, see Adverse Effects of Iron, p. 2074.1.

References.

1. Geisser P, Philipp E. PA21: a novel phosphate binder for the treatment of hyperphosphatemia in chronic kidney disease. *Clin Nephrol* 2010; 74: 4–11.
2. Wüthrich RP, *et al.* Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; 8: 280–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Velphoro.

Sugammadex Sodium

(BANM, USAN, rINNM)

Natrii Sugammadexum; Org-25969; Sugammadex sódico; Sugammadex Sodique; Натрий Сугаммадекс.

$C_{72}H_{104}Na_8O_{48}S_8$=2178.0

CAS — 343306-79-6.

ATC — V03AB35.

ATC Vet — QV03AB35.

UNII — ERJ6X2MXV7.

Uses and Administration

Sugammadex sodium is a modified gamma cyclodextrin that is a selective relaxant binding agent used for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. Sugammadex is given via an intravenous injection as the sodium salt, although doses are expressed in terms of the base. Sugammadex 100 mg is equivalent to about 108.78 mg sugammadex sodium.

For routine reversal of rocuronium- or vecuronium-induced blockade, a dose of 2 to 4 mg/kg sugammadex is recommended, depending on the depth of neuromuscular blockade. If re-occurrence of blockade occurs postoperatively, a repeat dose of 4 mg/kg sugammadex may be given.

For immediate reversal of rocuronium-induced blockade, a dose of 16 mg/kg sugammadex is recommended.

For doses in children, see below.

Reviews.

1. Nicholson WT, *et al.* Sugammadex: a novel agent for the reversal of neuromuscular blockade. *Pharmacotherapy* 2007; 27: 1181–8.
2. Welliver M, *et al.* Discovery, development, and clinical application of sugammadex sodium, a selective relaxant binding agent. *Drug Des Devel Ther* 2008; 2: 49–59.
3. Yang LPH, Keam SJ. Sugammadex: a review of its use in anaesthetic practice. *Drugs* 2009; 69: 919–42.
4. Plaud B. Le sugammadex: une nouveauté qui s'inscrit dans le cadre de l'amélioration de la sécurité des patients ou un simple gadget? *Ann Fr Anesth Reanim* 2009; 28 (suppl 2): S64–S69.
5. Kovac AL. Sugammadex: the first selective binding reversal agent for neuromuscular block. *J Clin Anesth* 2009; 21: 444–53.
6. Abrishami A, *et al.* Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 14/12/09).

Administration in children. Sugammadex sodium is used for the routine reversal of rocuronium-induced neuromuscular blockade in children and adolescents aged 2 to 17 years. Intravenous injection of 2 mg/kg sugammadex is recommended once recovery reaches an appropriate stage. For paediatric administration, sugammadex sodium can be diluted in sodium chloride 0.9%, to a concentration of 10 mg/mL.

Adverse Effects and Precautions

The most commonly reported adverse effect after use of sugammadex sodium is dysgeusia, which was mainly seen after high doses. Hypersensitivity reactions, including anaphylaxis, have occurred; reported symptoms include urticaria, erythematous rash, hypotension, tachycardia, and swelling of the tongue and pharynx. Bronchospasm has been reported rarely in patients with pulmonary complications.

Return of neuromuscular blockade has been reported, usually with suboptimal doses; respiratory function should be monitored until adequate spontaneous respiration is restored. If neuromuscular blockade is reversed during continued anaesthesia, additional doses of anaesthetic or opioid may be required if signs of inadequate anaesthesia occur.

Sugammadex is not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) due to a reduced clearance. Use is also not recommended in haemodialysis patients as clearance can be erratic. Patients with severe hepatic impairment should be treated with caution, as sugammadex has not been studied in this population.

Sugammadex should not be used to reverse block induced by nonsteroidal neuromuscular blockers such as suxamethonium chloride or benzylisoquinolinium compounds.

Activated partial thromboplastin time and prothrombin time may be slightly increased with sugammadex and caution is required in patients taking anticoagulants or those with pre-existing coagulopathies (see also Interactions, below).

Interactions

Although no interaction studies have been carried out, theoretically rocuronium or vecuronium could be displaced from the complex formed with sugammadex, resulting in re-occurrence of neuromuscular blockade. Toremifene may delay recovery if given on the same day as the operation. Fusidic acid may delay recovery if given pre-operatively, but is not expected to do so when given postoperatively. Rocuronium or vecuronium may also be displaced by flucloxacillin in intravenous doses of 500 mg or more, delaying recovery when given pre-operatively; such doses should be avoided for 6 hours postoperatively. When these drugs must be used within 6 hours of sugammadex, close monitoring for signs of neuromuscular blockade is recommended.

After reversal of blockade, rocuronium or vecuronium should not be given again for up to 16 hours, depending on the dose of sugammadex used and the intended dose of neuromuscular blocker (UK licensed product information recommends 24 hours). Patients with mild or moderate renal impairment require longer waiting times.

Sugammadex may slightly increase the activated partial thromboplastin time and the prothrombin time, and an additive effect has been noted *in vitro* with vitamin K antagonists, unfractionated heparin, low-molecular-weight heparins, rivaroxaban, and dabigatran. This interaction is not considered clinically relevant in patients on routine postoperative prophylactic anticoagulation, but caution is required in patients on therapeutic anticoagulants or those with pre-existing coagulopathies. If neuromuscular block-

ade is needed again within the recommended waiting time a nonsteroidal neuromuscular blocker should be used.

Sugammadex may interfere with serum progesterone assays.

Hormonal contraceptives. For information on the potential interaction between sugammadex and hormonal contraceptives, see Sugammadex, under Hormonal Contraceptives, p. 2244.1.

Pharmacokinetics

Neither sugammadex nor the complex it forms with rocuronium bind to plasma proteins or erythrocytes. Sugammadex is excreted by the kidneys, with 96% of a dose appearing in the urine, mainly as unchanged sugammadex. The elimination half-life in adults is about 2 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Bridion; *Austria*: Bridion; *Belg.*: Bridion; *Braz.*: Bridion; *Chile*: Bridion; *Cz.*: Bridion; *Denm.*: Bridion; *Fr.*: Bridion; *Ger.*: Bridion; *Gr.*: Bridion; *Hung.*: Bridion; *Irl.*: Bridion; *Israel*: Bridion; *Malaysia*: Bridion; *Neth.*: Bridion; *Norw.*: Bridion; *NZ*: Bridion; *Pol.*: Bridion; *Port.*: Bridion; *Rus.*: Bridan (Брай дан); *Spain*: Bridion; *Swed.*: Bridion; *Switz.*: Bridion; *Turk.*: Bridion; *UK*: Bridion; *Ukr.*: Bridion (Брайдан).

Tiopronin *(rINN)*

Thiopronine; Thioproninum; Tioproniini; Tiopronina; Tiopronine; Тиопронин.

N-(2-Mercaptopropionyl)glycine.

$C_5H_9NO_3S$=163.2

CAS — 1953-02-2.

ATC — R05CB12.

ATC Vet — QG04BC90; QR05CB12.

UNII — C5W04GO61S.

Uses and Administration

Tiopronin is a sulfhydryl compound and chelator with properties similar to those of penicillamine (p. 1567.1). It is given orally in the management of cystinuria (below), along with adequate hydration and alkalinisation of the urine, in usual doses of 0.8 to 1 g daily in divided doses. The dose should be adjusted according to the urinary cystine concentration; up to 2 g daily has been given. Tiopronin should be given on an empty stomach. Tiopronin is used in similar doses in rheumatoid arthritis. It has also been used in hepatic disorders and heavy-metal poisoning (including haemosiderosis and Wilson's disease) and formerly as a mucolytic. Tiopronin is being investigated as a neuroprotective agent in subarachnoid haemorrhage.

Cystinuria. Tiopronin may be used as an alternative to penicillamine in the management of cystinuria (p. 1567.2). A multicentre study[1] in 66 patients with cystine nephrolithiasis found that addition of tiopronin in doses of up to 2 g daily (mean 1.193 g) to standard alkali and fluid therapy significantly reduced urinary-cystine concentrations and the rate of new stone formation. Adverse effects were similar to those reported with penicillamine. In the 49 patients previously given penicillamine, it had produced adverse effects in 41, forcing therapy to be stopped in 34, whereas 37 had adverse effects with tiopronin, requiring drug withdrawal in 15. In the remaining 17 patients, 11 had adverse effects with tiopronin and 1 stopped treatment because of proteinuria. However, of the 34 patients who had been unable to tolerate penicillamine, 22 were able to continue treatment with tiopronin.

1. Pak CYC, *et al.* Management of cystine nephrolithiasis with alpha-mercaptopropionylglycine. *J Urol (Baltimore)* 1986; 136: 1003–8.

Rheumatoid arthritis. Tiopronin has been reported to have activity comparable to that of gold salts[1] and penicillamine[2] in patients with rheumatoid disease, and has been used to treat rheumatoid arthritis (p. 13.2), particularly in patients intolerant of penicillamine.

1. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; 7: 577–81.
2. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; 57: 105–11.

Unlike penicillamine, vitamin B_6 deficiency has occurred uncommonly with tiopronin.

Incidence of adverse effects. In a study of 140 patients[1] with rheumatoid arthritis receiving long-term treatment with tiopronin, adverse effects necessitated withdrawal of treatment in 56 patients (40%). The majority of adverse effects occurred within the first 6 months of treatment. The most common were those affecting the skin and mucous membranes (46 patients) including stomatitis, pruritus, erythema, and 1 case of pemphigus. Proteinuria developed in 5 patients and nephrotic syndrome in 3. Haematological disorders developed in 13 patients. Gastrointestinal disorders and ageusia were also reported.

In another study of 74 patients[2] with rheumatoid arthritis adverse effects were reported in 32 patients (43%) and necessitated withdrawal in 24%. The most common adverse effects were ageusia (21%), mucocutaneous lesions (16%), and gastrointestinal disturbances (14%). Haematological disorders occurred in 5 patients and proteinuria in 3 patients.

In a comparative study in 200 patients,[3] treatment was withdrawn due to toxicity in 27% of patients taking tiopronin and 21% of patients treated with gold.

1. Sany J, *et al.* Etude de la tolérance à long terme de la thiopronine (Acadione) dans le traitement de la polyarthrite rhumatoïde: a propos de 140 cas personnels. *Rev Rhum* 1990; 57: 105–11.
2. Ehrhart A, *et al.* Effets secondaires dus au traitement par la tiopronine de 74 polyarthrites rhumatoïdes. *Rev Rhum* 1991; 58: 193–7.
3. Ferraccioli GF, *et al.* Long-term outcome with gold thiosulphate and tiopronin in 200 rheumatoid patients. *Clin Exp Rheumatol* 1989; 7: 577–81.

Effects on the blood. Haematological disorders including leucopenia or thrombocytopenia have been reported during long-term studies of tiopronin. Isolated cases of agranulocytosis[1] and bone marrow aplasia[2] have also occurred.

See also Incidence of Adverse Effects, above.

1. Corda C, *et al.* Tiopronin-induced agranulocytosis. *Therapie* 1990; 45: 161.
2. Taillan B, *et al.* Aplasie médullaire au cours d'une polyarthrite rhumatoïde traitée par tiopronine. *Rev Rhum* 1990; 57: 443–4.

Effects on the kidneys. Proteinuria developed in 3 patients 4 to 14 months after starting treatment with tiopronin for cystinuria.[1] None of the patients had clinical symptoms of nephrotic syndrome. Renal biopsies in 2 patients showed membranous glomerulonephritis. Proteinuria disappeared in all 3 patients 4 to 5 months after tiopronin was discontinued. However, there was histological evidence of irreversible changes and signs of progressive glomerular lesions in 1 patient.

1. Lindell A, *et al.* Membranous glomerulonephritis induced by 2-mercaptopropionylglycine (2-MPG). *Clin Nephrol* 1990; 34: 108–15.

Effects on the skin. Mucocutaneous lesions are among the most common adverse effects of tiopronin (see Incidence of Adverse Effects, above). Reversible lichenoid eruptions have been reported[1] in a patient after treatment with tiopronin for 2 years, and may have been due to an immunological reaction to the sulfhydryl group. Lesions resembling pemphigus have also been reported in a few patients[2,3] and may require treatment with a corticosteroid or other immunosuppressant.

1. Kurumaji Y, Miyazaki K. Tiopronin-induced lichenoid eruption in a patient with liver disease and positive patch test reaction to drugs with sulfhydryl group. *J Dermatol* 1990; 17: 176–81.
2. Trona F, *et al.* Thiopronine-induced pemphigus vulgaris in rheumatoid arthritis. *Scand J Rheumatol* 1984; 13: 93–5.
3. Verdier-Sevrain S, *et al.* Thiopronine-induced herpetiform pemphigus: report of a case studied by immunoelectron microscopy and immunoblot analysis. *Br J Dermatol* 1994; 130: 238–40.

Pharmacokinetics

Tiopronin is absorbed from the gastrointestinal tract; peak plasma concentrations occur 3 to 6 hours after an oral dose. Up to 48% of the dose is reported to be excreted in the urine during the first 4 hours and up to 78% by 72 hours.

References.

1. Carlsson SM, *et al.* Pharmacokinetics of intravenous 2-mercaptopropionylglycine in man. *Eur J Clin Pharmacol* 1990; 38: 499–503.
2. Carlsson MS, *et al.* Pharmacokinetics of oral tiopronin. *Eur J Clin Pharmacol* 1993; 45: 79–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Chen Ji Ge (辰吉格); Ding Shu (丁舒); Hai Nuo Xin (海诺欣); Kai Na (凯纳); KaiXiLai (凯西莱); Kang Tong Su (康酮素); Libiqi (力比奇); Nuo Bai Li (诺百力); Nuoning (诺宁); Qie Ling Bao (切灵宝); Tong Da Rui (同达瑞); Wei Chun (维春); *Fr.*: Acadione; *Ger.*: Captimer; *Gr.*: Acadione; Thiola; *Ital.*: Thiola; Thiosolt; *USA*: Thiola.

Adverse Effects and Precautions

Tiopronin has similar adverse effects and precautions to those of penicillamine (p. 1568.1 and p. 1569.3) but reactions are generally fewer and less severe. Patients who have previously shown toxicity to penicillamine are more likely to develop adverse effects to tiopronin.

Trientine Dihydrochloride *(BAN, rINNM)*

Cuprid; Dihidrocloruro de trientina; MK-0681; TECZA (base or dihydrochloride); TETA (base or dihydrochloride); TJA-250; Trien Hydrochloride; Trientin Dihidroklorür; Trientina, dihidrocloruro de; Trientine, Dichlorhydrate de; Trientine Hydrochloride (USAN); Trientini Dihydrochloridum; Triethylenetetramine Dihydrochloride; Триентина Дигидрохлорид.

2,2'-Ethylenedi-iminobis(ethylamine) dihydrochloride; *N,N'*-bis(2-Aminoethyl)-1,2-ethanediamine dihydrochloride.

$C_6H_{18}N_4.2HCl$=219.2

CAS — 112-24-3 (trientine); 38260-01-4 (trientine dihydrochloride).

UNII — HC3NX54582.

Pharmacopoeias. In *US*.

USP 36: (Trientine Hydrochloride). A white to pale yellow crystalline powder. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether; soluble in methyl alcohol. pH of a 1% solution in water is between 7.0 and 8.5. Store under an inert gas in airtight containers at 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Trientine is a copper chelator used in the treatment of Wilson's disease (p. 1567.3). It tends to be used in patients intolerant of penicillamine.

Trientine dihydrochloride is given orally, preferably on an empty stomach. In the USA, the usual initial dose is 0.75 to 1.25 g daily in 2 to 4 divided doses; this may be increased to a maximum of 2 g daily if required. In the UK, a dose of 1.2 to 2.4 g daily, in 2 to 4 divided doses, has been recommended. For doses in children, see below.

Trientine is being studied in the prevention of macular oedema after eye procedures, and as an adjunct in cancer chemotherapy.

References.

1. Lu J. Triethylenetetramine pharmacology and its clinical applications. *Mol Cancer Ther* 2010; 9: 2458–67.

Administration in children. Trientine dihydrochloride is used in children for the treatment of Wilson's disease, particularly in those intolerant to penicillamine.[1] The initial oral dose in the USA is 500 or 750 mg daily in divided doses, increased if necessary to a maximum of 1.5 g daily. Doses are similar in the UK; for children aged 2 to 12 years, the *BNFC* suggests an oral dose of trientine dihydrochloride 600 mg to 1.5 g daily in 2 to 4 divided doses adjusted according to response. Older children can be given the usual adult dose (see above). The dose may be reduced and the frequency of dosing increased if nausea is a problem.

1. Taylor RM, *et al.* EuroWilson Consortium. Triethylene tetramine dihydrochloride (trientine) in children with Wilson disease: experience at King's College Hospital and review of the literature. *Eur J Pediatr* 2009; 168: 1061–8.

Adverse Effects and Precautions

Trientine may cause headache, dystonia, muscular spasm, myasthenia gravis, gastrointestinal disturbances, rash, and very rarely, anaemia, duodenitis, colitis, and rhabdomyolysis. Trientine can cause excessive excretion of trace metals such as zinc and iron; iron deficiency may occur, see also Interactions, below. Symptoms of SLE have recurred in a patient who had previously reacted to penicillamine. Hypersensitivity reactions including bronchospasm and dermatitis have occurred after prolonged environmental exposure in workers.

Pregnancy. Of 11 pregnancies in 7 women with Wilson's disease treated with trientine, 8 resulted in the delivery of a normal infant. One infant was premature and had a chromosomal defect, isochromosome X, there was one miscarriage associated with a contraceptive coil, and one elective termination. The average duration of treatment with trientine at the time of conception was almost 5 years and treatment was continued throughout pregnancy in most women. There was no significant copper depletion in the infants, and the 8 healthy infants developed normally during follow-up over 3 months to 9 years.[1]

1. Walshe JM. The management of pregnancy in Wilson's disease treated with trientine. *Q J Med* 1986; 58: 81–7.

Interactions

Trientine may be inactivated in the gastrointestinal tract by binding with metallic ions, and the absorption of iron may be impaired. Iron supplements should be taken at least 2 hours before or after trientine. Other mineral supplements may be similarly affected, and they should generally be avoided. It is recommended that trientine is taken on an empty stomach at least 1 hour apart from any other drug, food, or milk.

Pharmacokinetics

Trientine is rapidly but poorly absorbed from the gastrointestinal tract. Peak plasma concentrations occur up to about 2 hours after an oral dose. There is modest accumulation of trientine and its metabolites after repeated dosing, but it is not expected to be clinically significant. Trientine is extensively metabolised by acetylation with the majority of a dose excreted in the urine as metabolites. The average half-life is estimated to be around 2 to 4 hours.

References.
1. Cho H-Y, *et al.* Pharmacokinetic and pharmacodynamic modeling of a copper-selective chelator (TETA) in healthy adults. *J Clin Pharmacol* 2009; **49**: 916–28.
2. Lu J, *et al.* Pharmacokinetics, pharmacodynamics, and metabolism of triethyleneteramine in healthy human participants: an open-label trial. *J Clin Pharmacol* 2010; **50**: 647–58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Singapore*: Syprine; *USA*: Syprine.

Pharmacopoeial Preparations
USP 36: Trientine Hydrochloride Capsules.

Trimedoxime Bromide *(rINN)*

Bromuro de trimedoxima; Dipyroxime; TMB-4; Trimédoxime, Bromure de; Trimedoximi Bromidum; Триметоксима бромид.

1,1′-Trimethylenebis[4-formylpyridinium bromide]dioxime.

$C_{15}H_{18}Br_2N_4O_2$=446.1

CAS — 56-97-3.

UNII — EDOGXI9825.

NOTE. Do not confuse with Trimedoxine, a range of veterinary antibacterial preparations.

Profile

Trimedoxime bromide is a cholinesterase reactivator given with atropine in the treatment of organophosphorus poisoning.

References.
1. Kozer E, *et al.* Pediatric poisoning from trimedoxime (TMB4) and atropine automatic injectors. *J Pediatr* 2005; **146**: 41–4.
2. Bentur Y, *et al.* Civilian adult self injections of atropine-trimedoxime (TMB4) auto-injectors. *Clin Toxicol* 2006; **44**: 301–6.

Unithiol

DMPS; Unithiolum; Unitiol; Unitioli; Унитиол.

Sodium 2,3-dimercaptopropanesulfonate.

$C_3H_7NaO_3S_3$=210.3

CAS — 4076-02-2.

UNII — 690VN2L7TK.

Profile

Unithiol is a chelator structurally related to dimercaprol (p. 1549.3). It is water soluble and reported to be less toxic than dimercaprol. Unithiol is used in the treatment of poisoning by heavy metals including arsenic, lead, and inorganic and organic mercury compounds (see below).

In acute mercury poisoning an oral dose of unithiol 1.2 to 2.4 g daily is used. Oral doses are given in 100 to 200 mg portions evenly spaced over 24 hours. When unithiol cannot be given orally, intramuscular or slow intravenous injection can be used; a dose of 250 mg is given every 3 or 4 hours initially and then the frequency reduced daily to 250 mg every 8 to 24 hours from day 5 onwards. In chronic lead or mercury poisoning unithiol is given orally in a dose of 100 mg three or four times daily, increasing if required for severe toxicity.

The *National Poisons Information Service* in the UK prefers intravenous unithiol for the treatment of acute or chronic mercury poisoning, as the bioavailability of the oral formulation is low (about 40%); however, oral use may still be considered in less severe poisoning. A 5-day course of unithiol 30 mg/kg daily is recommended, given intravenously or orally in divided doses. A further treatment course may be considered if necessary based on blood- and urine-mercury concentrations. The same dose is recommended intravenously for the initial treatment of acute and chronic arsenic poisoning; treatment can be continued with oral unithiol once the patient has stabilised.

Reviews.
1. Hruby K, Donner A. 2,3-Dimercapto-1-propanesulphonate in heavy metal poisoning. *Med Toxicol* 1987; **2**: 317–23.
2. Aposhian HV, *et al.* Mobilization of heavy metals by newer, therapeutically useful chelating agents. *Toxicology* 1995; **97**: 23–38.

Arsenic poisoning. Complete recovery, without renal or neurological sequelae, has been reported[1,2] after use of unithiol in patients with potentially lethal acute arsenic poisoning; haemodialysis was also used in 1 patient.[2] Increased urinary arsenic excretion, with some improvement in clinical symptoms, has also been reported[3,4] with unithiol in chronic arsenic toxicity.

1. Moore DF, *et al.* Acute arsenic poisoning: absence of polyneuropathy after treatment with 2,3-dimercaptopropanesulphonate (DMPS). *J Neurol Neurosurg Psychiatry* 1994; **57**: 1133–5.
2. Kruszewska S, *et al.* The use of haemodialysis and 2,3 propanesulphonate (DMPS) to manage acute oral poisoning by lethal dose of arsenic trioxide. *Int J Occup Med Environ Health* 1996; **9**: 111–115.
3. Wax PM, Thornton CA. Recovery from severe arsenic-induced peripheral neuropathy with 2,3-dimercapto-1-propanesulphonic acid. *J Toxicol Clin Toxicol* 2000; **38**: 777–80.
4. Guha Mazumder DN, *et al.* Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *J Toxicol Clin Toxicol* 2001; **39**: 665–74.

Lead poisoning. Unithiol may be used in lead poisoning,[1] although other chelators are generally preferred (p. 2542.1). In a study of 12 children[2] it reduced lead concentrations in blood but did not affect the concentrations of copper or zinc in plasma, although the urinary excretion of lead, copper, and zinc was increased during treatment.

1. Aaseth J, *et al.* Treatment of mercury and lead poisonings with dimercaptosuccinic acid and sodium dimercaptopropanesulfonate: a review. *Analyst* 1995; **120**: 853–4.
2. Chisolm JJ, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. *J Pharmacol Exp Ther* 1985; **233**: 665–9.

Mercury poisoning. Unithiol is used in poisoning with mercury and mercury salts (p. 2556.3) and has been given by various routes. In 7 patients with poisoning due to mercury vapour or mercuric oxide, oral unithiol 100 mg given twice daily for up to 15 days enhanced urinary elimination of mercury;[1] the urinary elimination of copper and zinc was also increased in most patients and 2 developed rashes. A dose of 5 mg/kg intramuscularly three times daily, reduced to once daily by the third day of treatment, effectively reduced the half-life of mercury in the blood after poisoning with methylmercury.[2] A patient with severe mercuric chloride poisoning was treated successfully with unithiol given intravenously for 4 weeks, then orally for 3 weeks.[3] Unithiol has also been used with haemofiltration in patients with inorganic mercury poisoning and acute renal failure.[4,5] It has also proved useful in reversing the neurological symptoms associated with exposure to mercury vapour.[6]

1. Mant TGK. Clinical studies with dimercaptopropane sulphonate in mercury poisoning. *Hum Toxicol* 1985; **4**: 346.
2. Clarkson TW, *et al.* Tests of efficacy of antidotes for removal of methylmercury in human poisoning during the Iraq outbreak. *J Pharmacol Exp Ther* 1981; **218**: 74–83.
3. Toet AE, *et al.* Mercury kinetics in a case of severe mercuric chloride poisoning treated with dimercapto-1-propane sulphonate (DMPS). *Hum Exp Toxicol* 1994; **13**: 11–16.
4. Pai P, *et al.* Treatment of a case of severe mercuric salt overdose with DMPS (dimercapo-1-propane sulphonate [sic]) and continuous haemofiltration. *Nephrol Dial Transplant* 2000; **15**: 1889–90.
5. Dargan PI, *et al.* Case report: severe mercuric sulphate poisoning treated with 2,3-dimercaptopropane-1-sulphonate and haemodiafiltration. *Crit Care* 2003; **7**: R1–R6.
6. Bradberry SM, *et al.* DMPS can reverse the features of severe mercury vapor-induced neurological damage. *Clin Toxicol* 2009; **47**: 894–8.

Wilson's disease. Unithiol 200 mg twice daily[1] was used successfully to maintain cupriuresis in a 13-year-old boy with Wilson's disease (p. 1567.3) after he developed systemic lupus during treatment with penicillamine and with trientine dihydrochloride. Unithiol was started in 2 similar patients[1] but both withdrew from treatment, one because of fever and a fall in leucocyte count after a test dose and the other because of intense nausea and taste impairment.

1. Walshe JM. Unithiol in Wilson's disease. *BMJ* 1985; **290**: 673–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. Cz.: Dimaval; *Ger.*: Dimaval.

Contrast Media

Contrast media are widely used as adjuncts to diagnostic visualisation techniques such as radiography, magnetic resonance imaging, and ultrasound imaging. Although the techniques vary, they are all based on the fact that different tissues within the body have different physical properties, for example their ability to absorb radiation, or their density. These differences can be detected and used to produce images. Contrast media act in varying ways to accentuate the differences between tissues, and enhance the images obtained. There are different types of contrast medium, and choice depends upon the visualisation technique being used, as well as the properties of the individual media. The main groups described below are magnetic resonance contrast media, radiographic contrast media, and ultrasound contrast media.

Magnetic Resonance Contrast Media

Magnetic resonance imaging uses a combination of radiofrequency energy and magnetic fields to produce sectional images of the body. The technique is based on the property of hydrogen nuclei (protons) to absorb energy when aligned in a magnetic field; the energy is then released as the protons relax, generating a signal. Tissues differ in their proton content and factors affecting relaxation, and therefore produce different signals, which can be detected and analysed to produce an image.

Contrast media may be used to enhance magnetic resonance images. The media used are *paramagnetic* or *superparamagnetic* agents that develop magnetic properties when placed in a magnetic field. These properties affect the relaxation of adjacent protons during magnetic resonance imaging, and thus modify the signals produced. Paramagnetic compounds contain gadolinium or manganese and act by increasing relaxation and enhancing the signal. They are used as complexes or chelates to reduce their toxicity; gadopentetic acid is a typical gadolinium chelate, while mangafodipir is the only manganese chelate currently available. Superparamagnetic contrast media, such as ferucarbotran and ferumoxides, contain coated particles of iron compounds and act by interfering with the magnetic field to reduce the signal from proton relaxation.

References.

1. Sands MJ, Levitin A. Basics of magnetic resonance imaging. *Semin Vasc Surg* 2004; 17: 66–82.
2. Gibby WA. Basic principles of magnetic resonance imaging. *Neurosurg Clin N Am* 2005; 16: 1–64.
3. McGowan JC. Basic principles of magnetic resonance imaging. *Neuroimaging Clin N Am* 2008; 18: 623–36.

Radiographic Contrast Media

Radiography (including X-ray imaging, computed tomography, and fluoroscopy) is based on the difference between tissues in the extent to which they absorb X-rays. This depends largely on the density of the tissue, and increasing the difference, or contrast, between specific tissues can enhance the images produced. *Positive contrast* imaging is achieved by introducing a contrast medium into the area of interest to increase the density and enhance absorption of the X-rays. Alternatively, in *negative contrast* imaging, a gas (air, oxygen, or carbon dioxide) may be used to allow the X-rays to penetrate more easily. *Double contrast* uses both a gas and contrast medium together.

Radiographic contrast media are based on elements with high atomic numbers that absorb X-rays. The agents most commonly used are *iodinated organic compounds*, particularly *tri-iodinated benzene compounds*, and their degree of opacity or radiodensity is directly proportional to their iodine content. *Barium* is another element that absorbs X-rays, and barium sulfate has long been used in radiography. Other heavy atoms have been investigated but acute or chronic toxicity makes most of them unsuitable for use.

Iodinated contrast media may be classified as ionic or nonionic, and as monomeric or dimeric, and there are important differences between them that affect their use. The most important requirements for a contrast medium are that it absorbs X-rays efficiently, that it can be introduced into the area of the body to be visualised, and that it is safe. For iodinated contrast media, the radiodensity depends solely on the iodine concentration, whereas adverse effects are largely dependent on the osmolality of the solution (the number of particles present in a given weight of solution), with low-osmolality solutions being better tolerated. Distribution within the body depends on the pharmacokinetic and physical properties of the contrast medium.

Ionic monomeric media, such as the amidotrizoates, generally have a very high osmolality when given in concentrations suitable for radiographic visualisation, and therefore tend to be associated with a relatively high incidence of adverse effects. Osmolality may be reduced by using an *ionic dimeric* medium, such as adipiodone, which has twice the number of iodine atoms per molecule, or by using a *nonionic monomer*, such as iohexol, which does not dissociate into a cation and anion. *Nonionic dimeric* media, such as iodixanol, are also available and have the best ratio of radiodensity to osmolality; however, they also tend to be more viscous, and this may make them hard to use and affect distribution within the body.

References.

1. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; 209: 185–7.
2. Barrs TJ. X-rays and radiopaque drugs. *Am J Health-Syst Pharm* 2005; 62: 2026–30.

Ultrasound Contrast Media

Ultrasound imaging uses the acoustic properties of different tissues to produce images. Reflection of sound waves (echo) occurs at the interface between tissues with different acoustic properties, particularly where this difference is large, and this can be detected and analysed to produce images. Contrast agents are generally used to enhance the echogenicity of blood and therefore to enable measurement of blood flow in different parts of the body.

Ultrasound contrast media increase echogenicity by providing an interface that reflects sound. Although usually referred to as ultrasound contrast media or *echocontrast* media, the increase in echogenicity may in fact reduce contrast between tissues, and *echo-enhancers* may be a better term. Most ultrasound contrast media consist of microbubbles and provide a gas-liquid interface that reflects sound more effectively than blood alone, allowing blood flow to be more easily detected. The microbubbles may be air or another inert gas, such as perflutren or another perfluorocarbon, and may be either preformed or made at the time of injection. Agitated saline has been used as a simple ultrasound contrast medium, but is only suitable for cardiac imaging since the bubbles lack stability. Microbubbles of air formed during the dissolution of galactose are also used, and may be stabilised by addition of palmitic acid. Other stabilisers may be used, or the microbubbles may be encapsulated to increase the duration of their effect. Substances used for encapsulation include albumin (p. 1130.2) and phospholipids; polycyanoacrylates have also been investigated.

References.

1. Blomley MJK, *et al.* Microbubble contrast agents: a new era in ultrasound. *BMJ* 2001; 322: 1222–5.
2. Liang H-D, Blomley MJK. The role of ultrasound in molecular imaging. *Br J Radiol* 2003; 76 (special issue): S140–S150.
3. Dijkmans PA, *et al.* Microbubbles and ultrasound: from diagnosis to therapy. *Eur J Echocardiogr* 2004; 5: 245–56.
4. Dayton PA, Rychak JJ. Molecular ultrasound imaging using microbubble contrast agents. *Front Biosci* 2007; 12: 5124–42.
5. Klibanov AL. Ultrasound molecular imaging with targeted microbubble contrast agents. *J Nucl Cardiol* 2007; 14: 876–84.
6. Hauff P, *et al.* Ultrasound contrast agents for molecular imaging. In: Semmler W, Schwaiger M, eds. *Handb Exp Pharmacol: Molecular Imaging I.* Berlin: Springer-Verlag, 2008: 185 (I): 223–45.

Choice of Contrast Medium

Radiography, with and without the use of contrast, has been one of the most widely used diagnostic techniques and remains of great importance. However, concerns about the adverse effects of X-rays, and limitations of the images produced, have led to the increasing use of alternative methods such as ultrasound and magnetic resonance imaging. Choice of technique and use of contrast depends on the area to be visualised, the facilities available, and any patient characteristics affecting the likelihood of adverse effects, such as age and morbidity. Some imaging procedures and the factors affecting choice of technique and use of contrast, including adverse effects, are discussed below.

Uses of contrast media. For **urography** (visualisation of the kidneys and urinary tract) ultrasound is generally the most widely used technique, but radiography still has an important role. Contrast media that are excreted in the urine are used to enhance the images. Suitable media contain small, highly water-soluble molecules, with low protein-binding, that undergo rapid glomerular filtration and passage into the urinary tract. High plasma concentrations are needed to achieve adequate urinary concentrations for visualisation, so they are generally given intravenously. Most ionic iodinated media are suitable and the amidotrizoates have often been used, but lower-osmolality media are usually preferred since they have a lower incidence of adverse effects.

For **angiography** (visualisation of the circulatory system) radiography is still frequently used, particularly to produce dynamic images (fluoroscopy) during invasive procedures, although magnetic resonance angiography may be an alternative. Iodinated contrast media for angiography are similar to those used for urography; the main requirement is for a water-soluble molecule that will be rapidly distributed through the blood vessels. In addition, the solution should be of low viscosity to facilitate rapid injection and of high radiodensity to counteract the diluting effects of the blood. Low cardiotoxicity is particularly important for procedures that require a high concentration of contrast medium, such as angiocardiography or digital subtraction angiography, and low-osmolality media are now generally preferred for all angiographic procedures. Another widely used method for visualising the heart is echocardiography, which uses ultrasound imaging, and microbubble contrast media such as galactose or encapsulated gases (perfluorocarbons or sulfur hexafluoride) may be used to improve the images.

For **gastrointestinal imaging** endoscopy is often the preferred technique, but radiography also has a role. Positive, negative, and double contrast techniques are used. For positive contrast the contrast medium should not be absorbed but should form an even, homogeneous coat on the gastrointestinal mucosa, without interacting with gut secretions or producing misleading radiographic artefacts. The chief contrast medium for this purpose is barium sulfate, and much effort has been devoted to the production of suitable formulations to improve its coating properties and reduce the formation of bubbles, cracks, and other radiographic artefacts. Iodinated contrast media may be used as an alternative, but images tend to be inferior.

For **cholecystography** and **cholangiography** (visualisation of the gallbladder and biliary tract) ultrasound techniques have generally replaced radiography. Where radiography is used, choice of contrast medium depends on the intended procedure and the route. For intra-operative or endoscopic procedures, water-soluble contrast media may be used, but for non-invasive imaging the contrast medium used must be excreted in the bile. This requires a molecule with a free carboxy or other acidic group, since the biliary active transport mechanism is an anion transfer process; the molecule also needs to be large or highly protein-bound to prevent rapid excretion by the kidney. Suitable intravenous media include adipiodone and iotroxic acid. For oral use, absorption from the gastrointestinal tract is also required, and suitable media tend to be smaller molecules that are conjugated with glucuronic acid within the body before excretion in the bile, such as iopanoic acid. For visualisation of lesions within the liver itself, magnetic resonance imaging may be used; contrast media used to enhance the images include ferucarbotran and ferumoxides, as well as gadolinium or manganese chelates.

For **myelography** (visualisation of the structures of the spinal cord) and imaging of other parts of the CNS, magnetic resonance imaging is generally preferred, often with the use of gadolinium chelates such as gadopentetic acid as contrast media. Where radiography is used, the most important requirement for contrast media is low toxicity, and nonionic media are most common.

For **arthrography** (visualisation of the joint capsule) many radiographic contrast media are suitable provided they are well-diluted before use. Magnetic resonance imaging with gadolinium chelates may also have a role.

Bronchography (examination of the bronchial tree) has been performed with oily or aqueous media, such as iopydol or iopydone, instilled through a catheter or bronchoscope to coat the airways; however, other visualisation techniques are generally preferred.

For **hysterosalpingography** (visualisation of the uterus and fallopian tubes) ultrasound and endoscopic techniques are generally used, and microbubble contrast media such as galactose may be used to improve ultrasound images. If radiography is performed, water-soluble iodinated contrast media may be used.

For **lymphography** or **lymphangiography** (visualisation of the lymphatic system) a high radiodensity is required and the contrast medium must be retained within the lymphatic system for long enough to be visualised, requiring particulate, water-insoluble media, or very large molecules. Iodised oil has been most widely used, but adverse effects and limited distribution within the lymphatic system restrict its use.

Adverse effects of contrast media. Although contrast media are generally considered to be very safe, with most adverse effects being mild and transient, more severe and

even life-threatening reactions are possible, and the risk of adverse effects may influence the choice of contrast medium or imaging technique in a particular patient.

Iodinated **radiographic contrast media** all have a similar range of adverse effects (see under Amidotrizoic Acid, p. 1582.1) but the incidence and severity varies. Many of the adverse effects are related to the osmolality of the preparation, and the incidence tends to be lower with those that have low osmolality. Osmolality depends on the number of particles present in the solution; for a given iodine content, this is highest for the ionic monomers and lowest for nonionic dimers, and this is reflected in the incidence of adverse effects. Immediate hypersensitivity reactions also tend to be less frequent with nonionic media (see under Amidotrizoic Acid, p. 1583.1), although these reactions are not directly related to osmolality. However, low-osmolality media tend to be more expensive; while nonionics and dimers are preferred, ionic monomers may still have a role in patients at low risk of adverse effects. Ionic contrast media may also carry a lower risk of thromboembolism (see Effects on the Blood, p. 1582.1).

Magnetic resonance contrast media tend to be safer than iodinated contrast media, although similar general effects may occur. Ionic and nonionic media are available, but this tends to have little influence on the incidence of adverse effects. All gadolinium chelates have similar adverse effects (see under Gadopentetic Acid, p. 1586.2); there is a theoretical risk of gadolinium toxicity due to instability of the chelates and most preparations also contain free chelating agent to reduce this risk. The adverse effects of superparamagnetic iron compounds are described under ferumoxides (p. 1584.2) and ferumoxsil (p. 1584.3).

Ultrasound contrast media are generally safe; minor and transient adverse effects have been reported, but may be due to the procedure rather than to the contrast medium used. Some microbubble ultrasound contrast media such as perflutren (p. 1595.2) and sulfur hexafluoride (p. 1595.3) have been associated with more severe cardiopulmonary reactions.

References.

1. Thomsen HS, Bush WH. Adverse effects of contrast media: incidence, prevention and management. *Drug Safety* 1998; 19: 313–24.
2. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; 12: 205–13.
3. Maddox TG. Adverse reactions to contrast material: recognition, prevention, and treatment. *Am Fam Physician* 2002; 66: 1229–34.
4. Kirchin MA, Runge VM. Contrast agents for magnetic resonance imaging: safety update. *Top Magn Reson Imaging* 2003; 14: 426–35.
5. Christiansen C. X-ray contrast media—an overview. *Toxicology* 2005; 209: 185–7.
6. Jakobsen JA, *et al.* Safety of ultrasound contrast agents. *Eur Radiol* 2005; 15: 941–5.
7. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; 78: 686–93.
8. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. *Drug Safety* 2006; 29: 133–41.
9. European Society of Urogenital Radiology. ESUR guidelines on contrast media, version 7.0 (issued August 2008). Available at: http://www.esur.org/Guidelines_gallery.46.0.html (accessed 01/06/09)

Adipiodone *(BAN, rINN)*

Adipiodon; Adipiodona; Adipiodoni; Adipiodonum; Iodipamide; Адипиодон.

3,3′-Adipoylidiaminobis(2,4,6-tri-iodobenzoic acid).

$C_{20}H_{14}I_6N_2O_6$=1139.8

CAS — 606-17-7.

ATC — V08AC04.

ATC Vet — QV08AC04.

UNII — TKQ858A3VW.

Description. Adipiodone contains about 66.8% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Iodipamide). A white, practically odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Adipiodone *(rINNM)*

Adipiodona de meglumina; Adipiodone Meglumine (BANM); Adipiodone Méglumine; Diméglumine Iodipamide; Iodipamide Méglumine; Meglumine Iodipamide; Meglumini Adipiodonum; Меглумина Адипиодон.

The di(*N*-methylglucamine) salt of adipiodone.

$C_{20}H_{14}I_6N_2O_6.(C_7H_{17}NO_5)_2$=1530.2

CAS — 3521-84-4.

ATC — V08AC04.

ATC Vet — QV08AC04.

UNII — X064O0Y1A4.

Description. Meglumine adipiodone contains about 49.8% of I.

Pharmacopoeias. *US* includes only as an injection.

Incompatibility. Incompatibilities have been reported between meglumine adipiodone and some antihistamines.

Uses and Administration

Adipiodone is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is taken up by the liver and excreted in bile, and is used in cholangiography and cholecystography.

Adipiodone is given intravenously as a solution containing 52% of the meglumine salt. The usual dose is about 10 g of meglumine adipiodone, given by slow intravenous injection over about 10 minutes.

A solution of meglumine adipiodone with meglumine diatrizoate is given by intra-uterine instillation for hysterosalpingography.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. Rapid injection may increase the incidence of adverse effects.

Adipiodone may show some uricosuric activity.

Effects on the liver. Of 149 patients given the recommended dose of adipiodone, 13 developed elevated serum aspartate aminotransferase (SGOT) values; of 126 who received twice the dose, 23 developed elevated values.[1] Hepatotoxicity has also been reported[2-4] on isolated occasions in patients given meglumine adipiodone.

1. Scholz FJ, *et al.* Hepatotoxicity in cholangiography. *JAMA* 1974; 229: 1724.
2. Stillman AE. Hepatotoxic reaction to iodipamide meglumine injection. *JAMA* 1974; 228: 1420–1.
3. Sutherland LR, *et al.* Meglumine iodipamide (Cholografin) hepatotoxicity. *Ann Intern Med* 1977; 86: 437–9.
4. Imoto S. Meglumine hepatotoxicity. *Ann Intern Med* 1978; 88: 129.

Pharmacokinetics

Meglumine adipiodone is rapidly distributed in extracellular fluid after intravenous injection and is reported to be extensively bound to plasma proteins. It appears in the bile ducts within about 10 to 15 minutes after injection, with peak opacity at about 20 to 30 minutes, and reaches the gallbladder by about 1 hour, peak opacification occurring after about 2 hours. About 80 to 95% is excreted unchanged in the faeces; small amounts are excreted unchanged in urine. A terminal half-life of about 2 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Cholografin; *USA*: Cholografin.

Multi-ingredient Preparations. *Canad.*: Sinografin; *USA*: Sinografin.

Pharmacopoeial Preparations
BP 2014: Meglumine Iodipamide Injection;
USP 36: Iodipamide Meglumine Injection.

Amidotrizoic Acid *(BAN, rINNM)*

Acide Amidotrizoïque; Ácido amidotrizoico; Acidum Amidotrizoicum; Acidum Diatrizoicum; Amidotritsoiinihappo; Amidotrizoesäure-Dihydrat; Amidotrizoesav; Amidotrizoico, ácido; Amidotrizoinė rūgštis; Amidotrizoinsyra; Diatritsoiinihappo; Diatrizoic Acid (USAN); Diatrizoinsyra; Kyselina amidotrizoová; NSC-262168; Амидотризоевая Кислота.

3,5-Diacetamido-2,4,6-tri-iodobenzoic acid.

$C_{11}H_9I_3N_2O_4.2H_2O$=649.9

CAS — 117-96-4 (anhydrous amidotrizoic acid); 50978-11-5 (amidotrizoic acid dihydrate).

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — 5UVC90J1LK.

Description. Amidotrizoic acid contains about 62% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Amidotrizoic Acid Dihydrate). A white or almost white, crystalline powder. Very slightly soluble in water and in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Diatrizoic Acid). It is anhydrous or contains two molecules of water of hydration. A white, odourless, powder. Very slightly soluble in water and in alcohol; soluble in dimethylformamide and in alkali hydroxide solutions.

Meglumine Amidotrizoate *(BANM, rINNM)*

Amidotrizoate de Méglumine; Amidotrizoato de meglumina; Diatrizoate Meglumine; Meglumine Diatrizoate; Meglumini Amidotrizoas; Methylglucamine Diatrizoate; Меглумина Амидотризоат.

N-Methylglucamine 3,5-diacetamido-2,4,6-tri-iodobenzoate.

$C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$=809.1

CAS — 131-49-7.

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — 3X9MR4N98U.

Description. Meglumine amidotrizoate contains about 47.1% of I.

Pharmacopoeias. In *US.*

USP 36: (Diatrizoate Meglumine). A white, odourless, powder. Freely soluble in water. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Sodium Amidotrizoate *(BANM, rINN)*

Amidotrizoate de Sodium; Amidotrizoato de sodio; Diatrizoate Sodium; Natrii Amidotrizoas; Natrio amidotrizoatas; Natriumamidotritsoaatti; Natriumamidotrizoat; Natrium-amidotrizoät; Nátrium-amidotrizoát; NSC-61815; Sodium, amidotrizoate de; Sodium Diatrizoate; Sodu amidotrizoat; Натрия Амидотризоат.

Sodium 3,5-diacetamido-2,4,6-tri-iodobenzoate.

$C_{11}H_8I_3N_2NaO_4$=635.9

CAS — 737-31-5.

ATC — V08AA01.

ATC Vet — QV08AA01.

UNII — V5403H8VG7.

Description. Sodium amidotrizoate contains about 59.9% of I calculated on the anhydrous substance.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Chin. includes the injection.

Ph. Eur. 8: (Sodium Amidotrizoate). A white or almost white powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone. A 50% solution in water has a pH of 7.5 to 9.5. Protect from light.

USP 36: (Diatrizoate Sodium). A white, odourless, powder. Soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in ether.

Incompatibility. Incompatibilities of sodium amidotrizoate with some antihistamines have been reported.

Uses and Administration

The amidotrizoates are ionic monomeric iodinated radiographic contrast media (p. 1580.1). Both the sodium and the meglumine salt have been widely used in diagnostic radiography; however, adverse effects may be reduced by using a mixture of both salts, and this is often preferred. Preparations are available containing a wide range of strengths. Mixtures containing sodium amidotrizoate 10% w/v with meglumine amidotrizoate 66% w/v, or sodium amidotrizoate 4% with meglumine amidotrizoate 26%, are commonly used. For use alone, preparations containing sodium amidotrizoate 25 to 50% w/v, or meglumine amidotrizoate 60% w/v, may be appropriate.

The amidotrizoates are used in an extensive range of procedures, although in many cases lower osmolality contrast media are now preferred. The dose and route depend on the procedure and the degree and extent of contrast required. They are given intravenously for urography, for venography, and in computed tomography; for urography, they have also been given by intramuscular or subcutaneous injection, but these routes are not generally recommended. They may be given intra-arterially for angiography, by intra-articular injection for arthrography, or by intra-osseous injection for imaging of the vasculature of the bones. For other procedures they may be instilled into body cavities, or injected into the gallbladder, biliary ducts, or spleen. Amidotrizoates have also been given orally or rectally for imaging of the gastrointestinal tract.

Solutions of amidotrizoates have also been given as an enema in the treatment of uncomplicated meconium ileus.

Calcium amidotrizoate and lysine amidotrizoate have also been used as contrast media.

Gastrointestinal obstruction. Amidotrizoates and other water-soluble contrast media have been given rectally as osmotic agents in the management of gastrointestinal obstruction due to meconium ileus;[1] however, adverse effects have been reported in neonates (see p. 1583.2). They have also been used as an alternative to barium sulfate enemas in the management of intussusception (see under Barium Sulfate, p. 1583.3). Amidotrizoates given orally have been used in the management of adhesive

small bowel obstruction;[2] they allow identification of patients who require surgery and, although they have not been shown to relieve obstruction, they may reduce length of hospital stay in patients treated without surgery.

1. Murshed R, *et al.* Meconium ileus: a ten-year review of thirty-six patients. *Eur J Pediatr Surg* 1997; 7: 275–7.
2. Abbas S, *et al.* Oral water soluble contrast for the management of adhesive small bowel obstruction. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 14/07/08).

Adverse Effects and Treatment

Amidotrizoates and other iodinated contrast media may cause adverse effects due to direct toxicity, which tends to be dose-related and predictable, but use often leads to unpredictable or anaphylactoid reactions. Most reactions occur within 5 to 10 minutes and are mild and transient; however, severe, life-threatening reactions may also occur, and delayed reactions have been reported.

Direct toxic effects of iodinated contrast media are related to the osmolality of the solutions used and are most common with the amidotrizoates and other ionic monomeric compounds, which have a high osmolality. The route, the speed with which it is given, and the volume, concentration, and viscosity of the solution, also affect the incidence of adverse effects. For ionic media, the cation is also important: meglumine salts are generally better tolerated, but sodium salts have a lower viscosity and may produce fewer arrhythmias, and preparations containing a mixture of the salts are therefore often used. Anaphylactoid reactions are also more common with high-osmolality, ionic contrast media.

The most frequent direct adverse reaction to iodinated contrast media is flushing or a sensation of heat and caused by vasodilatation in response to the osmolality of the solution. Pain at the injection site is also common and extravasation may lead to tissue damage or thrombophlebitis.

General symptoms such as nausea, vomiting, headache, and dizziness may be related to patient anxiety or similar factors, or may be due to a mild anaphylactoid reaction. Urticaria, pruritus, pallor, sweating, a metallic taste, weakness, coughing, rhinitis, sneezing, lachrymation, and visual disturbances may also occur. Cardiovascular effects may also be due to direct toxicity, notably after intracoronary injection, or anaphylactoid response; they include hypotension, tachycardia, bradycardia, transient ECG abnormalities, and haemodynamic disturbances. More severe anaphylactoid reactions may lead to dyspnoea, bronchospasm, angioedema, severe urticaria, and eventually to profound hypotension, pulmonary oedema, respiratory arrest, ventricular fibrillation, circulatory failure, and cardiac arrest; fatalities have occurred.

CNS effects may result from direct toxicity, particularly after intrathecal use of ionic media or use in patients with a compromised blood-brain barrier, and can lead to severe neurotoxicity. Convulsions are more common in patients with epilepsy or brain tumours, but may also result from anaphylactoid reactions; paraesthesia, paralysis, and coma have also been reported.

Acute renal failure is an established adverse effect of contrast media, particularly in patients with predisposing factors such as dehydration (see Effects on the Kidneys (below), and Precautions, p. 1583.1). It appears to be related to the osmolality of the solution and is usually reversible, but deaths have occurred.

Iodinated contrast media also have direct effects on the blood, inhibiting blood coagulation and platelet aggregation. However, thromboembolism may also occur (see below). Disseminated intravascular coagulation and thrombocytopenia have also been reported.

Hyperthyroidism has been reported with use of iodinated contrast media, particularly in patients with goitre, and thyroid storm may be precipitated in patients with thyrotoxicosis. This is probably due to the small amounts of iodine present as a contaminant or released by any breakdown of the medium in the body. For the effects of iodine on the thyroid gland, see p. 2338.2.

Mild diarrhoea may follow the oral or rectal use of amidotrizoates for gastrointestinal examinations. Aspiration of oral solutions has caused fatal pulmonary oedema.

Adverse effects are treated symptomatically; adequate resuscitative facilities should be available when radiographic procedures are undertaken, and patients should be kept under observation for a suitable period after the procedure.

Effects on the blood. Iodinated contrast media affect blood coagulation to differing degrees.[1,2] Amidotrizoates and other ionic contrast media have inhibitory effects on blood coagulation and platelet aggregation, whereas nonionic media lack these effects. In procedures such as angiography, which are associated with a risk of thromboembolism, there may therefore be an advantage in using ionic media. However, the better overall tolerability of nonionic media means that they are still generally preferred to ionic media for angiography, particularly in patients at high risk of non-thromboembolic adverse effects.

Other effects on the blood that have been reported with amidotrizoates and other iodinated contrast media include disseminated intravascular coagulation,[3,4] haemolysis,[5] thrombocytopenia,[6,7] and thrombotic microangiopathy.[8]

1. Hussed SR, Kanstrup H. Thrombotic complications in coronary angioplasty—ionic versus non-ionic low-osmolar contrast media. *Acta Radiol* 1998; 39: 340–3.
2. Esplugas R, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; 25: 1079–98.
3. Lucas LM, *et al.* Case report: multisystem failure following intravenous iopamidol. *Clin Radiol* 1992; 45: 276–7.
4. Shigyo M, *et al.* A rare case of disseminated intravascular coagulation caused by the nonionic contrast medium iohexol. *J Urol (Baltimore)* 1995; 153: 1901–3.
5. Catterall JR, *et al.* Intravascular haemolysis with acute renal failure after angiocardiography. *BMJ* 1981; 282: 779–80.
6. Shojania AM. Immune-mediated thrombocytopenia due to an iodinated contrast medium (diatrizoate). *Can Med Assoc J* 1985; 133: 123.
7. Ural AU, *et al.* Thrombocytopenia following intravenous iopamidol. *Eur J Clin Pharmacol* 1998; 54: 575–6.
8. Fairley S, Ihle BU. Thrombotic microangiopathy and acute renal failure associated with arteriography. *BMJ* 1986; 293: 922–3.

Effects on the kidneys. Contrast nephropathy or contrast-induced nephrotoxicity is a well-established adverse effect of iodinated contrast media.[1-10] Estimates of the incidence vary depending on the type and amount of contrast medium used, the definition of nephropathy, and the population of patients being studied, but is about 1 to 6% overall. In the majority of patients who develop contrast-medium-induced renal impairment the condition develops within about 24 hours of the procedure, is asymptomatic, and resolves completely within about 10 days. However, the condition may occasionally be severe, producing oliguria and renal failure that requires dialysis; fatalities have occurred. A retrospective analysis[11] found that the development of contrast nephropathy was associated with increased 30-day mortality, and that this risk was higher in those given the contrast medium intravenously rather than intra-arterially.

The **mechanism** of nephrotoxicity is not certain, but is thought to involve both medullary hypoxia due to reduced renal blood flow, and direct toxicity. The osmolality of the contrast medium solution appears to be an important factor and most studies have shown that high-osmolality media increase the risk compared with low-osmolality media. There is also some evidence that use of media that are isosmolar with plasma may reduce the risk even further. The volume of contrast solution used is also important, and risk increases with higher volumes. The use of ionic or nonionic media appears to have less influence, except that nonionic media generally have a lower osmolality and may therefore be preferred.

The most important patient characteristic that increases the risk of nephrotoxicity is pre-existing renal impairment, especially in patients with diabetes mellitus. Other **risk factors** include conditions where there is reduced renal blood flow, such as heart failure and dehydration. Old age, repeated exposure (over a short period of time), multiple myeloma, and use with other nephrotoxic drugs, are also risk factors.

Various methods have been tried for **prophylaxis** of contrast medium-induced nephropathy.[1,3-10,12-14] All patients should be assessed for risk factors and those at high risk should be given a small volume of a low-osmolality or iso-osmolar nonionic medium if possible. *Hydration* before and after the procedure is of established benefit and is recommended in all patients, although the optimum route and fluid to use remains unclear. Oral hydration may be adequate in low risk patients, but most patients are given sodium chloride 0.45% or 0.9% intravenously. Sodium bicarbonate may be an alternative but the evidence is conflicting. Several studies have appeared to show an advantage for the use of sodium bicarbonate over sodium chloride in preventing contrast-induced nephropathy,[15-18] and a meta-analysis including these studies appeared to confirm the benefit.[19] However, it noted the risk of publication bias and study heterogeneity,[19] and others have found no advantage[20,21] or in one retrospective study even an increased risk[22] compared with no prophylaxis. Thus, although some protocols have suggested the use of bicarbonate-based hydration to prevent nephropathy,[23] further studies are needed to confirm its role.

Antioxidants have been suggested as a way of reducing the direct toxicity of contrast media. Acetylcysteine is widely used,[24] but again, evidence of benefit is conflicting. Some studies have produced promising results, but others have been less positive and, although reviews and meta-analyses have shown benefit[25,26] or a trend towards benefit,[27-29] this may reflect publication bias,[30] and most have concluded[24,26-29,31] that the wide variation between the studies included means that the efficacy of acetylcysteine remains uncertain. Later randomised studies have also reported conflicting results.[32,33] An observational study[34] found that there was no difference in the incidence of contrast nephropathy before and after the introduction of acetylcysteine prophylaxis, while a follow-up study[35] found that acetylcysteine had no effect on overall outcomes over 9 months. However, some authors[6,7,24] recommend the use of acetylcysteine in particularly high-risk patients. Ascorbic acid has also been tried and showed benefit in one study,[36] and promising results have been reported with trimetazidine, an anti-anginal drug with antioxidant properties,[37] but further confirmation is needed.

Other approaches have generally produced disappointing results.[1,3-7,10,12] The use of diuretics may increase the risk of nephropathy and is not recommended. Vasodilators have been tried, including atrial natriuretic peptide, calcium-channel blockers, low-dose dopamine, and alprostadil, but benefit has not been established and they are not generally used. Although positive results have been reported[38] with fenoldopam, which has preferential effects on renal blood flow, a large randomised study[39] failed to confirm any benefit. Studies with theophylline have produced conflicting results, although a meta-analysis[40] concluded that it might be of benefit. Use of dialysis to remove contrast medium from the circulation has also been suggested; some benefit has also been found with haemofiltration started before the procedure,[41] but not with haemodialysis immediately after the procedure.[42]

1. Esplugas E, *et al.* Comparative tolerability of contrast media used for coronary interventions. *Drug Safety* 2002; 25: 1079–98.
2. Rudnick MR, Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. *Rev Cardiovasc Med* 2003; 4 (suppl 5): S28–S33.
3. Cox CD, Tsikouris JP. Preventing contrast nephropathy: what is the best strategy? A review of the literature. *J Clin Pharmacol* 2004; 44: 327–37.
4. Maeder M, *et al.* Contrast nephropathy: review focusing on prevention. *J Am Coll Cardiol* 2004; 44: 1763–71.
5. Thomsen HS. How to avoid CIN: guidelines from the European Society of Urogenital Radiology. *Nephrol Dial Transplant* 2005; 20 (suppl 1): I18–I22. Also available at: http://ndt.oxfordjournals.org/cgi/reprint/20/suppl_1/I18.pdf (accessed 27/03/06)
6. Itoh Y, *et al.* Clinical and experimental evidence for prevention of acute renal failure induced by radiographic contrast media. *J Pharmacol Sci* 2005; 97: 473–88.
7. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. *Can Med Assoc J* 2005; 172: 1461–71. Correction. *ibid.*: 173: 1210.
8. Tepel M, *et al.* Contrast-induced nephropathy: a clinical and evidence-based approach. *Circulation* 2006; 113: 1799–1806.
9. Pannu N, *et al.* Prophylaxis strategies for contrast-induced nephropathy. *JAMA* 2006; 295: 2765–79.
10. Massicotte A. Contrast medium-induced nephropathy: strategies for prevention. *Pharmacotherapy* 2008; 28: 1140–50.
11. From AM, *et al.* Mortality associated with nephropathy after radiographic contrast exposure. *Mayo Clin Proc* 2008; 83: 1095–1100.
12. Lepor NE. A review of pharmacologic interventions to prevent contrast-induced nephropathy. *Rev Cardiovasc Med* 2003; 4 (suppl 5): S34–S42.
13. Barrett BJ, Parfrey PS. Preventing nephropathy induced by contrast medium. *N Engl J Med* 2006; 354: 379–86.
14. Kelly AM, *et al.* Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; 148: 284–94. Correction *ibid.*: 149: 219.
15. Merten GJ, *et al.* Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized controlled trial. *JAMA* 2004; 291: 2328–34.
16. Masuda M, *et al.* Comparison of usefulness of sodium bicarbonate versus sodium chloride to prevent contrast-induced nephropathy in patients undergoing an emergent coronary procedure. *Am J Cardiol* 2007; 100: 781–6.
17. Briguori C, *et al.* Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation* 2007; 115: 1211–17.
18. Ozcan EE, *et al.* Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy: a comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J* 2007; 154: 539–44.
19. Hogan SE, *et al.* Current role of sodium bicarbonate-based preprocedural hydration for the prevention of contrast-induced acute kidney injury: a meta-analysis. *Am Heart J* 2008; 156: 414–21.
20. Brar SS, *et al.* Sodium bicarbonate vs sodium chloride for the prevention of contrast medium-induced nephropathy in patients undergoing coronary angiography: a randomized trial. *JAMA* 2008; 300: 1038–46.
21. Zoungas S, *et al.* Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med* 2009; 151: 631–8.
22. From AM, *et al.* Sodium bicarbonate is associated with an increased incidence of contrast nephropathy: a retrospective cohort study of 7977 patients at Mayo Clinic. *Clin J Am Soc Nephrol* 2008; 3: 10–18.
23. Goldfarb S, *et al.* Contrast-induced acute kidney injury: specialty-specific protocols for interventional radiology, diagnostic computed tomography radiology, and interventional cardiology. *Mayo Clin Proc* 2009; 84: 170–9.
24. Pisbhane S, *et al.* N-acetylcysteine in the prevention of radiocontrast-induced nephropathy. *J Am Soc Nephrol* 2004; 15: 251–60.
25. Birck R, *et al.* Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; 362: 598–603.
26. Bagshaw SM, Ghali WA. Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. *BMC Med* 2004; 2: 38.
27. Pannu N, *et al.* Systematic review of the impact of N-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; 65: 1366–74.
28. Nallamothu BK, *et al.* Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004; 117: 938–47.
29. Zagler A, *et al.* N-acetylcysteine and contrast-induced nephropathy: a meta-analysis of 13 randomized trials. *Am Heart J* 2006; 151: 140–5.
30. Vaitkus PT, Brar C. N-acetylcysteine in the prevention of contrast-induced nephropathy: publication bias perpetuated by meta-analyses. *Am Heart J* 2007; 153: 275–80.
31. Kshirsagar AV, *et al.* N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; 15: 761–9.
32. Coyle LC, *et al.* Acetylcysteine In Diabetes (AID): a randomized study of acetylcysteine for the prevention of contrast nephropathy in diabetics. *Am Heart J* 2006; 151: 1032.e9–1032.e12.

33. Marenzi G, *et al.* N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. *N Engl J Med* 2006; 354: 2773–82.
34. Shah SJ, Hsu C-Y. Has acetylcysteine use changed the incidence of contrast nephropathy in hospitalized patients? A before-after study. *Am J Med* 2004; 117: 948–52.
35. Miner SES, *et al.* N-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J* 2004; 148: 690–5.
36. Spargias K, *et al.* Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; 110: 2837–42.
37. Onbasili AO, *et al.* Trimetazidine in the prevention of contrast-induced nephropathy after coronary procedures. *Heart* 2007; 93: 698–702.
38. Chu VL, Cheng JWM. Fenoldopam in the prevention of contrast media-induced acute renal failure. *Ann Pharmacother* 2001; 35: 1278–82. Correction. *ibid.*: 1677.
39. Stone GW, *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA* 2003; 290: 2284–91.
40. Bagshaw SM, Ghali WA. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Arch Intern Med* 2005; 165: 1087–93.
41. Marenzi G, *et al.* The prevention of radiocontrast-agent-induced nephropathy by hemofiltration. *N Engl J Med* 2003; 349: 1333–40.
42. Vogt B, *et al.* Prophylactic hemodialysis after radiocontrast media in patients with renal insufficiency is potentially harmful. *Am J Med* 2001; 111: 692–8.

Hypersensitivity. Anaphylactoid reactions to iodinated contrast media are more common with the ionic agents than the nonionic media of lower osmolality. Patients at increased risk are those with a history of asthma or allergy, drug hypersensitivity, adrenal suppression, heart disease, previous reaction to a contrast medium, and those receiving beta blockers or interleukin-2 therapy. In such patients, nonionic media are preferred. Stopping treatment with beta blockers should be considered in patients with other risk factors.

Pretreatment with corticosteroids may be considered for preventing anaphylactoid reactions in high-risk patients, and an antihistamine may also be given. However, reactions may still occur and the value of premedication remains controversial.

Patients may also experience delayed type-IV hypersensitivity reactions, usually manifesting as mild to moderate maculopapular rash, urticaria, and angioedema. For unknown reasons, unlike immediate reactions, these may be more common with nonionic dimeric contrast media.

References.
1. Canter LM. Anaphylactoid reactions to radiocontrast media. *Allergy Asthma Proc* 2005; 26: 199–203.
2. Idée J-M, *et al.* Allergy-like reactions to iodinated contrast agents: a critical analysis. *Fundam Clin Pharmacol* 2005; 19: 263–81.
3. Morcos SK. Acute serious and fatal reactions to contrast media: our current understanding. *Br J Radiol* 2005; 78: 686–93.
4. Tramèr MR, *et al.* Pharmacological prevention of serious anaphylactic reactions due to iodinated contrast media: systematic review. Abridged version: *BMJ* 2006; 333: 675–8. Full version: http://www.bmj.com/cgi/reprint/333/7570/675 (accessed 05/09/08)
5. Meth MJ, Maibach HI. Current understanding of contrast media reactions and implications for clinical management. *Drug Safety* 2006; 29: 133–41.

Precautions

The risk of anaphylactoid reactions with amidotrizoates and other iodinated contrast media is increased in patients with asthma or a history of allergies and they should be used with great caution in such patients; they should not be used in patients with a previous reaction to contrast media or iodine. Test doses have been given but are not generally recommended since they do not predict hypersensitivity with certainty and may cause severe or fatal reactions. Pretreatment with corticosteroids may be considered in patients considered at high risk of reactions, but the value of this is uncertain (see Hypersensitivity, above). An antihistamine may be given with the corticosteroid.

Iodinated contrast media should be used with caution in patients with severe hepatic or renal impairment, diabetics with renal impairment, and others who may be at increased risk of renal failure. Dehydration should be avoided, and any fluid or electrolyte imbalance should be corrected before contrast media are given. Particular care is needed in patients with multiple myeloma since dehydration resulting from use of contrast media may cause precipitation of protein in the renal tubules, leading to anuria and fatal renal failure.

Caution is also necessary in patients with severe hypertension, advanced cardiac disease, phaeochromocytoma, sickle-cell disease, or hyperthyroidism or epilepsy, and in debilitated, severely ill, very old, or very young patients.

Amidotrizoates and other hypertonic contrast media are neurotoxic and should not be given intrathecally; patients with subarachnoid haemorrhage may be at risk with any intravascular use. Intravascular contrast media should also be used with caution in any patient with occlusive vascular disease. Iodinated contrast media should not be used for hysterosalpingography in the presence of infection or inflammation of the pelvic cavity, nor during menstruation or in pregnancy (although any abdominal radiography should be avoided during pregnancy because of the risks of radiation to the fetus).

Iodine-containing contrast media may interfere with thyroid function tests. There may also be interference with blood coagulation tests and certain urine tests.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving amidotrizoates and the American Academy of Pediatrics considers[1] that they are therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Neonates. Although amidotrizoates may be used in the management of some forms of intestinal obstruction (see p. 1581.3), meglumine amidotrizoate was considered[1] a possible contributory factor in the deaths of 2 infants who developed bowel necrosis, perforation, and peritonitis after its use for meconium ileus.

1. Leonidas JC, *et al.* Possible adverse effects of methylglucamine diatrizoate compounds on the bowel of newborn infants with meconium ileus. *Radiology* 1976; 121: 693–6.

Pharmacokinetics

Amidotrizoates are very poorly absorbed from the gastrointestinal tract. Amidotrizoates in the circulation are not significantly bound to plasma proteins. If renal function is not impaired, unchanged amidotrizoate is rapidly excreted by glomerular filtration; over 95% of an intravascular dose is reported to be excreted in urine within 24 hours, and about 1 to 2% of a dose may be excreted in faeces. Trace amounts may be detected in other body fluids including tears and saliva. Faecal excretion may increase to 10 to 50% in severe renal impairment. The half-life of amidotrizoates has been reported to be 30 to 60 minutes, which can increase to 20 to 140 hours in severe renal impairment. They are removed by haemodialysis and peritoneal dialysis.

The amidotrizoates cross the placenta and are distributed into breast milk.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Angiografina; Densopax; Gastropaque Iodo; MD-76; MD-Gastroview; Plenigraf; Temistac; Tomoray 76C; Triyosom; Urografina; Urovisona; X-Graf C; X-Graf; *Austral.*: Gastrografin; MD-76†; MD-Gastroview; Urografin; *Austria*: Gastrografin; Peritrast; *Belg.*: Gastrografin; Urografine; *Braz.*: Hypaque-M; Hypaque; Urografina; *Canad.*: Gastrografin; Hypaque-M†; Hypaque†; MD-76†; Reno-Dip†; Reno†; Renocal†; *Chile*: Angiovist†; Reliev 76%; Reliev; *China*: Angiografin (格纳芬); *Denm.*: Urografin; *Fin.*: Gastrografin; *Fr.*: Gastrografine; Radioselectan; *Ger.*: Ethibloc†; Gastrografin; Gastrolux; Peritrast; Urolux Retro; *Gr.*: Gastrografin; Urografin; *Hung.*: Gastrografin; Peritrast; *India*: Angiografin; Urografin; *Irl.*: Urografin; *Ital.*: Gastrografin; *Neth.*: Gastrografin; Urografin; *Norw.*: Gastrografin; *NZ*: Gastrografin; Urografin; *Port.*: Gastrografina; Urografina; *Rus.*: Trazograph (Тразограф); Triombrast (Триомбраст); Urografin (Урографин); *S.Afr.*: Gastrografin; Urografin; *Spain*: Gastrografin; Pielograf†; Plenigraf; Radialar 280; Trazograf†; Uro Angiografin†; Urografin; *Swed.*: Gastrografin; Urografin†; *Switz.*: Gastrografin; Gastrolux; *Turk.*: Urografin; Urovideo; Urovist-Angiografin; *UK*: Gastrografin; Hypaque; Urografin 150; *Ukr.*: Trazograph (Тразограф)†; *USA*: Cystografin; Gastrografin; Hypaque-M, Hypaque-76†; Hypaque†; MD-76; MD-Gastroview; Reno-M†; Renografin†.

Multi-ingredient Preparations. *Canad.*: Sinografin; *India*: Contrastin; *Irl.*: Gastrografin; *USA*: Sinografin.

Pharmacopoeial Preparations

BP 2014: Meglumine Amidotrizoate Injection;
USP 36: Diatrizoate Meglumine and Diatrizoate Sodium Injection; Diatrizoate Meglumine and Diatrizoate Sodium Solution; Diatrizoate Meglumine Injection; Diatrizoate Sodium Injection; Diatrizoate Sodium Solution.

Barium Sulfate

Barii sulfas; Barii Sulphas; Bario sulfatas; Barium Sulfuricum; Barium Sulphate; Bariumsulfaatti; Bariumsulfat; Bárium-szulfát; Baru siarczan; Baryum (Sulfate de); Baryum, sulfate de; Síran bárnatý; Sulfato de bario; Сульфат бария.

$BaSO_4$=233.4

CAS — 7727-43-7

ATC Vet — QV08BA02

UNII — 25BB7EKE2E

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Barium Sulfate). A fine, white powder, free from gritty particles. Practically insoluble in water and in organic solvents; very slightly soluble in acids and in solutions of alkali hydroxides.

USP 36: (Barium Sulfate). A fine, white, odourless, bulky powder, free from grittiness. Practically insoluble in water, in organic solvents, and in solutions of acids and of alkalis. pH of a 10% w/w aqueous suspension is between 3.5 and 10.0.

Uses and Administration

Barium sulfate is used as a radiographic contrast medium (p. 1580.1) for X-ray examination of the gastrointestinal tract involving single- or double-contrast techniques or computed tomography.

The dose of barium sulfate is dependent upon the type of examination and technique used. In the UK typical doses and concentrations used for examination are:

- oesophagus: up to 150 mL of a 50 to 200% w/v suspension given orally
- stomach and duodenum: up to 300 mL of a 30 to 200% w/v suspension given orally
- small intestine: 100 to 300 mL of a 30 to 150% w/v suspension given orally
- colon: 200 mL to 2 litres of a 20 to 130% w/v suspension given as an enema

A suspension containing 1.2 to 2.2% may be used in gastrointestinal computed tomography.

In the USA, suspensions containing up to 230% w/v barium sulfate may be used; lower concentrations are available for use in computed tomography and usually contain about 1 to 2% w/v.

For double-contrast examination, gas can be introduced into the gastrointestinal tract by using suspensions of barium sulfate containing carbon dioxide; separate gas-producing preparations based on sodium bicarbonate are also available. Air given via a tube may be used as an alternative to carbon dioxide.

Reviews.
1. Nolan DJ, Traill ZC. The current role of the barium examination of the small intestine. *Clin Radiol* 1997; 52: 809–20.
2. Mendelson RM. The role of the barium enema in the diagnosis of colorectal neoplasia. *Australas Radiol* 1998; 42: 191–6.
3. de Zwart IM, *et al.* Barium enema and endoscopy for the detection of colorectal neoplasia: sensitivity, specificity, complications and its determinants. *Clin Radiol* 2001; 56: 401–9.
4. Rubesin SE, Maglinte DD. Double-contrast barium enema technique. *Radiol Clin North Am* 2003; 41: 365–76.
5. O'Connor SD, Summers RM. Revisiting oral barium sulfate contrast agents. *Acad Radiol* 2007; 14: 72–80.
6. Canon CL. Is there still a role for double-contrast barium enema examination? *Clin Gastroenterol Hepatol* 2008; 6: 389–92.

Intussusception. Contrast media enemas and ultrasound are both used in the diagnosis of intussusception, a condition in infants where part of the intestine prolapses into the lumen of an adjacent part causing an obstruction.[1-3] However, some consider ultrasound to be superior for diagnosis and reserve enemas for the therapeutic reduction of intussusception. Reduction is achieved as a result of the hydrostatic pressure of the enema pushing the intestine back into its natural position. Although there is extensive experience using barium enemas for reduction some centres prefer to use water-soluble contrast media so as to minimise the risk of chemical peritonitis if perforation of the bowel occurs. Other agents used instead of barium for reduction include air enemas or ultrasound guided saline enemas, both of which avoid or reduce radiographic exposure. Surgery is indicated when enema therapy fails or is considered unsuitable.

1. del-Pozo G, *et al.* Intussusception in children: current concepts in diagnosis and enema reduction. *Radiographics* 1999; 19: 299–319.
2. Sorantin E, Lindbichler F. Management of intussusception. *Eur Radiol* 2004; 14 (suppl 4): L146–L154.
3. Waseem M, Rosenberg HK. Intussusception. *Pediatr Emerg Care* 2008; 24: 793–800.

Adverse Effects

Because barium sulfate is almost insoluble it lacks the severe toxicity characteristic of the barium ion; deaths have occurred in patients given the more soluble barium sulfide in error for the sulfate.

Constipation may occur after oral or rectal barium sulfate; impaction, obstruction, and appendicitis have occurred. Surgical removal of faecaliths has sometimes been necessary. Cramping or diarrhoea have also been reported. Venous intravasation has led to the formation of emboli; deaths have occurred. Perforation of the bowel has led to peritonitis, adhesions, granulomas, and a high mortality rate.

ECG abnormalities have occurred during the use of barium sulfate enemas.

Accidental aspiration into the lungs has led to pneumonitis or granuloma formation.

Hypersensitivity. A survey of hypersensitivity reactions to barium preparations found that although barium is inert many of the additives used in formulation have the potential to cause reactions.[1] Of 106 reactions reported or found

in the literature, 61% involved the skin and only 8% the respiratory tract; unconsciousness was reported in 8% of cases. In view of the frequency of use of barium preparations, such adverse reactions must be very rare, but radiologists should be aware that they might be somewhat more common than was usually appreciated. A number of severe reactions associated with the use of barium enemas supplied with an inflatable latex cuff may have been due to leaching of components from the latex.[2]

1. Janower ML. Hypersensitivity reactions after barium studies of the upper and lower gastrointestinal tract. *Radiology* 1986; 161: 139–40.
2. Nightingale SL. Severe adverse reactions to barium enema procedures. *JAMA* 1990; 264: 2863.

Precautions

Barium sulfate should not be given to patients with intestinal obstruction and care is needed in those with conditions such as pyloric stenosis or lesions that may predispose to obstruction. Adequate hydration should be ensured after the procedure to prevent severe constipation.

It is contra-indicated in patients with gastrointestinal perforation, and should be avoided, particularly when given rectally, in those at risk of perforation, such as patients with acute ulcerative colitis or diverticulitis and after rectal or colonic biopsy, sigmoidoscopy, or radiotherapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies barium sulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Barigraf; Bario; Bariofarma; Barosperse†; E-Z-Cat; Entero VU; Gastropaque; Novopac; Opti-Up; Scheribar; Tixobar; Top-Cat; *Austral.*: Medebar†; Medescan†; *Austria*: Micropaque; Prontobario; Scannotrast; *Belg.*: E-Z-Paque; Micropaque; Microtrast; Polibar; *Braz.*: Bariogel; *Canad.*: Anatrast†; Baricon†; Barobag†; Barocat†; Barosperse†; Cheetah†; Enhancer†; Enterovu†; Entrobar†; Entroease†; Esobar†; Esopho-Cat†; Flo-Coat†; Intropaste†; Liqui-Coat HD†; Medebar Plus†; Polibar Liquid†; Polibar Plus†; Polibar Rapid†; Prepcat†; Readi-Cat†; Ultra-R†; Unibar†; *China*: Bei Ying (倍影); Cz.: E-Z-Cat; E-Z-HD; Micropaque; Microtrast†; Polibar; *Denm.*: Micropaque†; Microtrast; Mixobar; Unicat; *Fin.*: Mixobar; *Fr.*: Micropaque; Microtrast; *Ger.*: Barilux; Micropaque; Microtrast; *Gr.*: Barilux; Micropaque; Polibar ACB; Unibaryt-R; *Hung.*: E-Z-Cat; E-Z-HD; Micropaque; Microtrast; Polibar Rapid†; Polibar; *Irl.*: Baricat; Maxibar; Polibar; *Israel*: E-Z-Cat; E-Z-HD; E-Z-Paque; Entero VU; Polibar ACB; Polibar Plus†; *Ital.*: Prontobario; TAC Esofago; *Neth.*: Baricol; E-Z-Cat; E-Z-HD; Micropaque; Polibar; *Norw.*: Mixobar; *Port.*: E-Z-Cat; E-Z-HD; Gastrobario; Micropaque; Microtrast; Polibar; *Rus.*: Bar-VIPS (Бар-ВИПС); *Spain*: Barigraf; Barilux; Bario Dif†; Disperbarium†; *Swed.*: Mixobar; *Switz.*: CAT-Barium (E-Z-CAT); Microbar-HD (E-Z-HD); Micropaque; Polibar ACB; *Thai.*: Solotop; *Turk.*: Bar-X-Ray; E-Z-Cat; E-Z-HD; Opti-Up; Polibar; R-X; Radyobarit; *Ultrabarit*; *UK*: Baritop; E-Z-Cat; E-Z-HD; E-Z-Paque; Polibar Rapid; Polibar; *USA*: Anatrast†; Baricon†; Barocat; Barobag†; Barosperse†; Bear-E-Yum; CheeTah†; Digibar; E-Z-HD; E-Z-Paque; E-Z-Paste; Enecat; Enemark; Enhancer†; Entero VU; Entrobar†; Epi-C; Flo-Coat†; HD 200 Plus†; HD 85†; Intropaste†; Liqui-Coat HD†; Liquipake; Medebar†; Medescan; Polibar; Prepcat†; Readi-Cat; Scan C†; Tomocat†; Tonojug†; Tonopaque†; Varibar; *Venez.*: Barin.

Multi-ingredient Preparations. *Turk.*: Radyobarit-Double Contrast.

Pharmacopoeial Preparations
BP 2014: Barium Sulphate for Suspension; Barium Sulphate Oral Suspension;
USP 36: Barium Sulfate for Suspension; Barium Sulfate Paste; Barium Sulfate Suspension; Barium Sulfate Tablets.

Ferristene *(BAN, USAN)*

Ferristeno; Ферристен.
$C_6H_{11}NO_5S(Fe_2O_3)_{n?2?5}$
CAS — 155773-56-1.
ATC — V08CB02.
ATC Vet — QV08CB02.

Description. Ferristene contains about 23.4% of Fe.

Profile

Ferristene consists of iron ferrite crystals carried on monosized spheres of cross-linked poly(ammonium styrenesulfonate). It has superparamagnetic properties and has been used orally as a magnetic resonance contrast medium (p. 1580.1) for imaging of the abdomen.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Abdoscan.

Ferucarbotran *(BAN, USAN)*

Ferrixan; Ferucarbotrano; SHU-555A; ZK-132281.

Profile

Ferucarbotran is a colloidal aqueous suspension of iron oxide (magnetite and maghemite) particles coated with carboxydextran. It has superparamagnetic properties and is used similarly to ferumoxides (below) as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is given intravenously as a solution containing 28 mg/mL of iron. The usual dose is 0.9 mL for patients weighing less than 60 kg and 1.4 mL for patients weighing 60 kg and over.

References.

1. Reimer P, Balzer T. Ferucarbotran (Resovist): a new clinically approved RES-specific contrast agent for contrast-enhanced MRI of the liver: properties, clinical development, and applications. *Eur Radiol* 2003; 13: 1266–76.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Resovist; *Belg.*: Resovist†; *Cz.*: Resovist†; *Fr.*: Cliavist†; *Ger.*: Resovist†; *Gr.*: Resovist; *Ital.*: Resovist; *Neth.*: Resovist†; *Norw.*: Resovist†; *Port.*: Resovist†; *Spain*: Resovist†; *Swed.*: Resovist†; *Switz.*: Resovist†.

Ferumoxides *(BAN, USAN)*

AMI-25; Ferumóxidos.
$(Fe_2O_3)_m(FeO)_n$
CAS — 119683-68-0.
UNII — G6N3J0SWB4.

Uses and Administration

Ferumoxides consists of colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver; the particles are taken up by the reticuloendothelial system of the liver and spleen and provide contrast enhancement. It is available as a suspension containing 11.2 mg/mL of iron, which should be diluted in 100 mL of glucose 5% before use and given intravenously over at least 30 minutes. The dose is expressed in terms of iron. In Europe, the usual dose is 840 micrograms/kg; in the USA, a dose of 560 micrograms/kg is used.

Reference to the use of ferumoxides followed by a gadolinium-based contrast medium.[1]

1. Qayyum A, *et al.* Detection of hepatocellular carcinoma by ferumoxides-enhanced MR imaging in cirrhosis: incremental value of dynamic gadolinium-enhancement. *J Magn Reson Imaging* 2006; 23: 17–22.

Adverse Effects and Precautions

The most common adverse effects with ferumoxides are pain, vasodilatation, and hypotension; paraesthesia may also occur. Hypersensitivity reactions have developed. Extravasation may lead to discoloration of the skin around the injection site. Ferumoxides should not be used in patients with known hypersensitivity to iron and should be used with caution in patients with iron overload disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Endorem; *Belg.*: Endorem†; *Denm.*: Endorem†; *Fin.*: Endorem†; *Fr.*: Endorem†; *Ger.*: Endorem†; *Gr.*: Endorem; *Irl.*: Endorem; *Ital.*: Endorem; *Jpn*: Feridex†; *Neth.*: Endorem†; *Norw.*: Endorem†; *Port.*: Endorem; *Spain*: Endorem†; *Swed.*: Endorem†; *Switz.*: Endorem†; *Turk.*: Endorem; *USA*: Feridex.

Pharmacopoeial Preparations
USP 36: Ferumoxides Injection.

Ferumoxsil *(BAN, USAN)*

AMI-121; Ferumoksiili; Ferumoxil; Férumoxsil; Ferumoxsilum; Ферумоксил.
CAS — 171544-35-7.
ATC — V08CB01.
ATC Vet — QV08CB01.
UNII — 6HJV9H13XS.

Uses and Administration

Ferumoxsil consists of a silicone polymer bonded to colloidal particles of magnetite (iron oxide). It has superparamagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the gastrointestinal tract; the particles remain in the stomach and intestine when given orally or rectally and provide contrast enhancement. It is given as a suspension containing 175 micrograms/mL of iron. The usual dose is 600 to 900 mL orally, or 300 to 600 mL rectally.

Adverse Effects and Precautions

The most common adverse effects with ferumoxsil are diarrhoea, nausea, vomiting, and abdominal pain; oral paraesthesia has also been reported. Ferumoxsil should be used with caution in patients with iron overload disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Lumirem; *Denm.*: Lumirem; *Fin.*: Lumirem; *Fr.*: Lumirem; *Ger.*: Lumirem; *Ital.*: Lumirem; *Neth.*: Lumirem; *Port.*: Lumirem; *Swed.*: Lumirem; *USA*: Gastromark.

Pharmacopoeial Preparations
USP 36: Ferumoxsil Oral Suspension.

Ferumoxtran-10 *(USAN)*

AMI-227; BMS-180549; Code 7227.
CAS — 189047-99-2.

Profile

Ferumoxtran-10 consists of colloidal particles of magnetite (iron oxide) coated with a low-molecular-weight dextran. It has superparamagnetic properties and has been investigated as a magnetic resonance contrast medium for imaging of the lymphatic system.

Gadobenic Acid *(BAN, rINN)*

Acide Gadobénique; Ácido gadobénico; Acidum Gadobenicum; B-19036; Gadobénico, ácido; Gd-BOPTA; Гадобеновая Кислота.
Dihydrogen [(±)-4-carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2-oxa-5,8,11-triazatridecan-13-oato(5-)]gadolinate(2-).
$C_{22}H_{28}GdN_3O_{11}$=667.7
CAS — 113662-23-0.
ATC — V08CA08.
ATC Vet — QV08CA08.

Meglumine Gadobenate *(BANM, rINNM)*

B-19036/7; Gadobenaattidimeglumiini; Gadobenatdimeglumin; Gadobénate de Méglumine; Gadobenate Dimeglumine (USAN); Gadobenato de meglumina; Gadobenatum Dimegluminum; Meglumini Gadobenas; Меглумина Гадобенат.
$C_{22}H_{28}GdN_3O_{11}.2C_7H_{17}NO_5$=1058.2
CAS — 127000-20-8.
ATC — V08CA08.
ATC Vet — QV08CA08.
UNII — 3Q6PPC19PQ.

Uses and Administration

Gadobenic acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the liver and CNS, and in magnetic resonance angiography to detect narrowing or obstruction of the abdominal or peripheral arteries.

Gadobenic acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadobenate 529 mg/mL (0.5 mmol/mL). Usual doses by body-weight for imaging are:

- liver: 0.1 mL/kg (0.05 mmol/kg)
- brain or spine: 0.2 mL/kg (0.1 mmol/kg)
- angiography: 0.2 mL/kg (0.1 mmol/kg)

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

References.

1. Kirchin MA, *et al.* Safety assessment of gadobenate dimeglumine (MultiHance): extended clinical experience from phase I studies to post-marketing surveillance. *J Magn Reson Imaging* 2001; 14: 281–94.

2. Shellock FG, *et al.* Safety of gadobenate dimeglumine (MultiHance): summary of findings from clinical studies and postmarketing surveillance. *Invest Radiol* 2006; 41: 500–9.

Pharmacokinetics

Gadobenate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of about 1.2 to 1.7 hours has been reported. It is not metabolised and about 78 to 94% of a dose is excreted in the urine within 24 hours; about 2 to 4% is excreted in the faeces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: MultiHance; ***Austria***: MultiHance; ***Belg.***: MultiHance; ***Canad.***: MultiHance; ***China***: MultiHance (莱迪司); ***Cz.***: MultiHance; ***Denm.***: MultiHance; ***Fin.***: MultiHance; ***Fr.***: MultiHance; ***Ger.***: MultiHance; ***Gr.***: MultiHance; ***Hung.***: MultiHance; ***Irl.***: MultiHance; ***Israel***: MultiHance; ***Ital.***: MultiHance; ***Neth.***: MultiHance; ***Norw.***: MultiHance; ***NZ***: MultiHance; ***Port.***: MultiHance; ***Singapore***: MultiHance; ***Spain***: MultiHance; ***Swed.***: MultiHance; ***Switz.***: MultiHance; ***Turk.***: MultiHance; ***UK***: MultiHance; ***USA***: MultiHance.

Gadobutrol *(USAN, rINN)*

Gadobutrolum; ZK-135079; Гадобутрол.

(10-[(1*RS*,2*SR*)-2,3-Dihydroxy-1-(hydroxymethyl)propyl]-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)]gadolinium.

$C_{18}H_{31}GdN_4O_9$=604.7

CAS — 138071-82-6; 770691-21-9.

ATC — V08CA09.

ATC Vet — QV08CA09.

UNII — 1BJ477IO2L.

NOTE. Protovist is a trade mark that has been used for gadobutrol.

Uses and Administration

Gadobutrol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of the CNS, kidneys, and liver, and in magnetic resonance angiography.

Gadobutrol is available as a solution containing 605 mg/mL (1 mmol/mL). It is given intravenously. Usual doses for adults by body-weight are:

- cranial and spinal imaging: 0.1 mL/kg (0.1 mmol/kg). A second dose of up to 0.2 mL/kg (0.2 mmol/kg) may be given within 30 minutes if required
- kidneys and liver: 0.1 mL/kg (0.1 mmol/kg)
- angiography: 0.1 to 0.3 mL/kg (0.1 to 0.3 mmol/kg)

Children aged 7 years and older and adolescents may be given 0.1 mL/kg (0.1 mmol/kg) for all the above indications. This dose may also be given to children aged 2 years and older in CNS imaging.

A solution containing 302.5 mg/mL (0.5 mmol/mL) has also been used.

References.

1. Huppertz A, Rohrer M. Gadobutrol, a highly concentrated MR-imaging contrast agent: its physicochemical characteristics and the basis for its use in contrast-enhanced MR angiography and perfusion imaging. *Eur Radiol* 2004; 14 (suppl 5): M12–M18.

Administration in children. Gadobutrol is licensed in the UK for imaging of the CNS, kidneys, and liver, and in magnetic resonance angiography, in children aged 7 years and older. In the USA, gadobutrol may be used for CNS imaging in children aged 2 years and older. For doses, see Uses and Administration, above.

See also under Pharmacokinetics, below.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2. Gadobutrol may prolong cardiac repolarisation and should not be used in patients with uncorrected hypokalaemia. Caution is required in patients with severe cardiovascular disease, and in those with congenital long QT syndrome or a history of drug-induced arrhythmias.

General references.

1. Forsting M, Palkowitsch P. Prevalence of acute adverse reactions to gadobutrol—a highly concentrated macrocyclic gadolinium chelate: review of 14,299 patients from observational trials. *Eur J Radiol* 2010; 74: e186–e192.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadobutrol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

Gadobutrol is rapidly distributed into the extracellular space after intravenous injection. It is not significantly bound to plasma proteins. An elimination half-life of about 1.8 hours has been reported. It is not metabolised and more than 90% of a dose is excreted in the urine within 12 hours; less than 0.1% is excreted in the faeces.

References.

1. Hahn G, *et al.* Pharmacokinetics and safety of gadobutrol-enhanced magnetic resonance imaging in pediatric patients. *Invest Radiol* 2009; 44: 776–83.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Gadovist; ***Austria***: Gadovist; ***Belg.***: Gadovist; ***Braz.***: Gadovist; ***Canad.***: Gadovist; ***China***: Gadovist (加乐显); ***Cz.***: Gadovist; ***Denm.***: Gadovist; ***Fin.***: Gadovist; ***Fr.***: Gadovist; ***Ger.***: Gadovist; ***Gr.***: Gadovist; ***Hung.***: Gadovist; ***Irl.***: Gadovist; ***Ital.***: Gadovist; ***Neth.***: Gadovist; ***Norw.***: Gadovist; ***NZ***: Gadovist; ***Port.***: Gadovist; ***Rus.***: Gadovist (Гадовист); ***S.Afr.***: Gadovist; ***Spain***: Gadovist; ***Swed.***: Gadovist; ***Switz.***: Gadovist; ***Turk.***: Gadovist; ***UK***: Gadovist; ***USA***: Gadavist.

Gadodiamide *(BAN, USAN, rINN)*

Gadodiamid; Gadodiamida; Gadodiamidi; Gadodiamidum; GdDTPA-BMA; S-041; Гадодиамид.

[*N*,*N*-Bis(2-{(carboxymethyl)[(methylcarbamoyl)methyl]amino}ethyl)glycinato(3-)]gadolinium; a complex of gadolinium with diethylenetriamine penta-acetic acid bismethylamide.

$C_{16}H_{26}GdN_5O_8$=573.7

CAS — 131410-48-5 (anhydrous gadodiamide); 122795-43-1 (gadodiamide hydrate).

ATC — V08CA03.

ATC Vet — QV08CA03.

UNII — 84F6U3J2R6.

Pharmacopoeias. In *US*.

USP 36: (Gadodiamide). A white, odourless, powder. Freely soluble in water and in methyl alcohol; soluble in alcohol; slightly soluble in acetone and in chloroform. Store in airtight containers.

Uses and Administration

Gadodiamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures, imaging of the whole body, angiography and evaluation of cardiac perfusion (stress/rest testing and late enhancement), and mammography.

Gadodiamide is available as a solution containing 287 mg/mL (0.5 mmol/mL). Usual intravenous doses by body-weight are:

- cranial and spinal imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg). Adults may be given a second dose of 0.4 mL/kg (0.2 mmol/kg) within 20 minutes if required
- whole body imaging: for adults and children, 0.2 mL/kg (0.1 mmol/kg)
- kidneys: for adults and children, 0.1 mL/kg (0.05 mmol/kg) may be adequate
- angiography: for adults, 0.2 mL/kg (0.1 mmol/kg)
- cardiac perfusion in coronary artery disease: for adults, 0.3 mL/kg (0.15 mmol/kg). For stress/rest testing, this is given rapidly in 2 equally divided doses 10 minutes or more apart, the first dose being accompanied by a pharmacological stress agent given via a separate intravenous line
- mammography: 0.2 to 0.4 mL/kg (0.1 to 0.2 mmol/kg)

Liposomal gadodiamide is under investigation for the adjunctive treatment of glioma, by aiding visualisation of the distribution of the antineoplastic topotecan.

Administration in children. Gadodiamide is licensed for use in children from 2 years of age in both the EU and the USA; it is used for cranial and spinal imaging and whole body imaging. For doses see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2. Inadvertent intrathecal use of gadodiamide has resulted in convulsions, coma, and deficits of sensory and motor nerve function.

Effects on the pancreas. Acute pancreatitis developed in a patient shortly after injection of gadodiamide for hepatic imaging.[1] Another patient[2] developed both acute pancreatitis and acute renal failure after use of gadodiamide for angiography.

1. Terzi C, Sökmen S. Acute pancreatitis induced by magnetic-resonance-imaging contrast agent. *Lancet* 1999; 354: 1789–90. Correction. *Ibid.* 2000; 355: 660.
2. Schenker MP, *et al.* Gadolinium arteriography complicated by acute pancreatitis and acute renal failure. *J Vasc Interv Radiol* 2001; 12: 393.

Interference with diagnostic tests. Gadodiamide may interfere with colorimetric methods for measuring serum calcium concentrations, resulting in falsely low measurements. Severe pseudohypocalcaemia has been reported[1-3] after the use of gadodiamide, particularly in patients with renal impairment.[2] There is also *in vitro* evidence that a similar interference may occur with gadoversetamide.[2]

1. Doorenbos CJ, *et al.* Severe pseudohypocalcemia after gadolinium-enhanced magnetic resonance angiography. *N Engl J Med* 2003; 349: 817–18.
2. Prince MR, *et al.* Gadodiamide administration causes spurious hypocalcemia. *Radiology* 2003; 227 639–46.
3. Williams SP, *et al.* Spurious hypocalcemia after gadodiamide administration. *Mayo Clin Proc* 2005; 80: 1655–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadodiamide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Renal impairment. For the view that gadodiamide may carry a particular risk of the development of nephrogenic systemic fibrosis in patients with renal impairment, see p. 1586.3.

Pharmacokinetics

Gadodiamide is rapidly distributed into extracellular fluid. About 96% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 70 minutes has been reported. Gadodiamide is not bound to plasma proteins. It is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Omniscan; ***Austral.***: Omniscan; ***Austria***: Omniscan; ***Belg.***: Omniscan; ***Canad.***: Omniscan; ***Chile***: Omniscan; ***China***: Omniscan (欧乃影); ***Cz.***: Omniscan; ***Denm.***: Omniscan; ***Fin.***: Omniscan; ***Fr.***: Omniscan; ***Ger.***: Omniscan; ***Gr.***: Omniscan; ***Hung.***: Omniscan; ***Irl.***: Omniscan; ***Israel***: Omniscan; ***Ital.***: Omniscan; ***Jpn***: Omniscan; ***Neth.***: Omniscan; ***Norw.***: Omniscan; ***NZ***: Omniscan; ***Port.***: Omniscan; ***Rus.***: Omniscan (Омнискан); ***Spain***: Omniscan; ***Swed.***: Omniscan; ***Switz.***: Omniscan; ***Turk.***: Omniscan; ***UK***: Omniscan; ***Ukr.***: Omniscan (Омнискан); ***USA***: Omniscan.

Pharmacopoeial Preparations

USP 36: Gadodiamide Injection.

Gadofosveset Trisodium *(BANM, USAN, rINNM)*

Gadofosveset trisódico; Gadofosvéset Trisodique; Gadofosvesetum Trinatricum; MS-325 (gadofosveset); MS-32520; Тринатрий Гадофосвезет.

Trisodium (*N*-[2-[bis(carboxymethyl)amino]ethyl]-*N*-{(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl}glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6-))gadolinate(3-).

$C_{33}H_{38}GdN_3Na_3O_{14}P$=957.9

CAS — 201688-00-8 (gadofosveset); 193901-90-5 (gadofosveset trisodium).

ATC — V08CA11.

ATC Vet — QV08CA11.

UNII — XM33Q67UVH (gadofosveset trisodium); 9430ZR8ZAN (anhydrous gadofosveset trisodium).

Profile

Gadofosveset is a gadolinium chelate used as a paramagnetic contrast medium (p. 1580.1) in magnetic resonance angiography. It binds to plasma proteins, particularly albumin, and therefore acts as a blood pool agent, allowing visualisation of the vasculature.

Gadofosveset is given by intravenous injection as the trisodium salt. It is available as a solution containing gadofosveset trisodium 244 mg/mL (0.25 mmol/mL). The usual dose is 0.12 mL/kg (0.03 mmol/kg).

References.

1. Henness S, Keating GM. Gadofosveset. *Drugs* 2006; 66: 851–7.
2. Goyen M. Gadofosveset-enhanced magnetic resonance angiography. *Vasc Health Risk Manag* 2008; 4: 1–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Ablavar; *Belg.*: Vasovist†; *Canad.*: Ablavar; Vasovist; *Cz.*: Ablavar; *Denm.*: Vasovist†; *Fr.*: Vasovist†; *Ger.*: Ablavar†; *Gr.*: Ablavar†; *Hung.*: Vasovist; *Ital.*: Vasovist†; *Neth.*: Ablavar†; *Norw.*: Ablavar†; *Pol.*: Vasovist; *Port.*: Ablavar; *Spain*: Ablavar†; *Swed.*: Ablavar†; *Switz.*: Vasovist†; *Turk.*: Vasovist; *UK*: Ablavar; *USA*: Ablavar.

Gadopentetic Acid *(BAN, rINN)*

Acide Gadopentétique; Ácido gadopentético; Acidum Gadopenteticum; Gadolinium-DTPA; Gadopentético, ácido; Гадопентетовая Кислота.

Dihydrogen *(N,N*-bis[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-))gadolinate(2-); a complex of gadolinium with diethylenetriamine penta-acetic acid.

$C_{14}H_{20}GdN_3O_{10}$=547.6

CAS — 80529-93-7.

ATC — V08CA01.

ATC Vet — QV08CA01.

UNII — K2I13DR72L.

Meglumine Gadopentetate *(BANM, rINNM)*

Dimeglumine Gadopentetate; Gadopentétate de Méglumine; Gadopentetate Dimeglumine (USAN); Gadopentetate Meglumine; Gadopentétate méglumine; Gadopentetato de meglumina; Meglumini Gadopentetas; SH-L-4S1-A; Мегглумина Гадопентетат.

$C_{14}H_{20}GdN_3O_{10}(C_7H_{17}NO_5)_2$=938.0

CAS — 86050-77-3.

ATC — V08CA01.

ATC Vet — QV08CA01.

UNII — RH248G8V27.

Pharmacopoeias. *Chin.* and *US* include only as an injection.

Uses and Administration

Gadopentetic acid is an ionic gadolinium chelate used as a contrast medium in magnetic resonance imaging (p. 1580.1). Gadolinium has paramagnetic properties that affect the relaxivity of hydrogen ions, increasing the signal intensity and therefore enhancing the contrast between tissues. Chelation of gadolinium reduces its toxicity while retaining its paramagnetic properties; it also affects distribution within the body. Most gadolinium chelates distribute freely into extracellular fluid but do not cross the blood-brain barrier, and they are particularly useful for imaging the brain and associated structures.

Gadopentetic acid is given intravenously as meglumine gadopentetate for contrast enhancement in magnetic resonance imaging of cranial and spinal structures, and of the whole body, it has also been used for evaluation of renal function. It is given by intra-articular injection for arthrography, and has been used orally and rectally in imaging of the gastrointestinal tract.

For cranial, spinal, and whole body imaging, a solution containing meglumine gadopentetate 469.01 mg/mL (0.5 mmol/mL) is used in the following usual doses by body-weight:

- cranial and spinal imaging: for adults and children aged over 1 month, 0.2 mL/kg (0.1 mmol/kg) (but see also Precautions, below). A further dose of 0.2 mL/kg (0.1 mmol/kg) may be given within 30 minutes to adults and children aged over 1 year if necessary; in adults this second dose may be 0.4 mL/kg (0.2 mmol/kg). In special circumstances a dose of 0.6 mL/kg (0.3 mmol/kg) may be used in adults.
- whole body imaging: for adults and children aged over 1 month, 0.2 mL/kg (0.1 mmol/kg); in adults and children aged over 1 year a dose of 0.4 mL/kg (0.2 mmol/kg) may be needed in some cases to produce adequate contrast and in special circumstances a dose of 0.6 mL/kg (0.3 mmol/kg) may be used in adults.

For arthrography a solution containing meglumine gadopentetate 1.876 mg/mL (0.002 mmol/mL) is given to adults by intra-articular injection. The dose depends on the joint being imaged; the usual range is from 1 to 20 mL although up to 50 mL may be given into the knee.

For imaging of the gastrointestinal tract a solution containing meglumine gadopentetate 9.38 mg/mL has been used, diluted further before use.

Administration in children. Gadopentetate is licensed in the UK for use in cranial and spinal imaging and whole body imaging in children (but see also Precautions, below). For doses, see Uses and Administration, above.

Adverse Effects

There may be headache, nausea, vomiting, dizziness, and transient sensations of heat or cold or taste disturbances on injection of gadopentetate or other gadolinium chelates. Rarely, convulsions, hypotension, allergic or anaphylactoid reactions, and shock may occur. Paraesthesias and localised pain have also been reported. Transient elevations of serum iron and bilirubin values have been observed. Nephrogenic systemic fibrosis may occur rarely in patients with renal impairment (see under Precautions, below).

General references.

1. Nelson KL, *et al.* Clinical safety of gadopentetate dimeglumine. *Radiology* 1995; 196: 439–43.

Effects on the nervous system. Subacute encephalopathy has been reported[1] in a woman who was given repeated doses of a gadolinium chelate for magnetic resonance imaging. It was suggested that renal impairment may have contributed to retention of gadolinium, with subsequent diffusion into the CSF.

1. Maramattom BV, *et al.* Gadolinium encephalopathy in a patient with renal failure. *Neurology* 2005; 64: 1276–8.

Hypersensitivity. Although rare, anaphylactoid reactions have occurred with a number of gadolinium chelates.[1] Severe reactions have been reported with gadopentetate,[2] gadoterate,[3,4] and gadoteridol,[3] including a fatal reaction with gadopentetate.[6] There has also been a report[7] of a severe reaction with gadoteridol in a patient who had previously tolerated gadopentetate. Reactions may occur despite premedication with antihistamines and corticosteroids.[8] Since such reactions are unpredictable, UK licensed product information for gadolinium chelates recommends that facilities for resuscitation should be readily available when they are used.

1. Runge VM. Safety of approved MR contrast media for intravenous injection. *J Magn Reson Imaging* 2000; 12: 205–13.
2. Tardy B, *et al.* Anaphylactic shock induced by intravenous gadopentetate dimeglumine. *Lancet* 1992; 339: 494.
3. Meuli RA, Maeder P. Life-threatening anaphylactoid reaction after IV injection of gadoterate meglumine. *Am J Roentg* 1996; 166: 729.
4. Beaudouin E, *et al.* Anaphylactic shock induced by gadoterate meglumine (DOTAREM). *Allerg Immunol (Paris)* 2003; 35: 382–5.
5. Shellock FG, *et al.* Adverse reaction to intravenous gadoteridol. *Radiology* 1993; 189: 151–2.
6. Jordan RM, Mintz RD. Fatal reaction to gadopentetate dimeglumine. *Am J Roentg* 1995; 164: 743–4.
7. Witte RJ, Anzai LL. Life-threatening anaphylactoid reaction after intravenous gadoteridol administration in a patient who had previously received gadopentetate dimeglumine. *Am J Neuroradiol* 1994; 15: 523–4.
8. Dillman JR, *et al.* Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *Am J Roentg* 2008; 190: 187–90.

Precautions

Gadopentetate and other gadolinium chelates should not be used in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2) or with acute renal impairment associated with hepato-renal syndrome or liver transplantation (see Renal Impairment, below). It should be given with care to patients with moderate renal impairment, epilepsy, hypotension, or a history of hypersensitivity, asthma, or other allergic respiratory disorders. Although, with the exception of neonates, gadopentetate is licensed in the UK for use in infants under 1 year of age, it should be used with caution because of their immature renal function (see also Children, below). US licensed product information considers that safety and efficacy have not been demonstrated in those under 2 years of age. Some other gadolinium chelates may not be licensed for use in children (see under the individual monographs). Studies *in vitro* suggest a theoretical risk that enhancement of magnetic moment by gadolinium chelates might induce vaso-occlusive symptoms in patients with sickle-cell disease, but clinical evidence is lacking. Care should be taken to avoid extravasation. Gadopentetate may interfere with tests of serum iron or bilirubin concentrations.

Breast feeding. Studies[1-3] have shown that gadopentetate is distributed into breast milk in very small amounts; the total amount excreted in the milk within 24 hours was less than 0.04% of the intravenous dose in all cases. No adverse effects have been seen in breast-feeding infants whose mothers were receiving gadopentetic acid and the American Academy of Pediatrics considers[4] that it is therefore usually compatible with breast feeding. However, to minimise the risk of nephrogenic systemic fibrosis associated with gadolinium chelates in breast-feeding infants, the EMEA's Committee for Medicinal Products for Human Use[5] (CHMP) advises mothers to stop breast feeding for at least 24 hours after the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide). The decision of whether to continue or suspend breast feeding for 24 hours after the use of medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agents (gadobutrol, gadoterate, and gadoteridol) should be made in consultation with the mother.

1. Schmiedl U, *et al.* Excretion of gadopentetate dimeglumine in human breast milk. *Am J Roentg* 1990; 154: 1305–6.
2. Rofsky NM, *et al.* Quantitative analysis of gadopentetate dimeglumine excreted in breast milk. *J Magn Reson Imaging* 1993; 3: 131–2.
3. Kubik-Huch RA, *et al.* Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology* 2000; 216: 555–8.
4. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)
5. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; 3 (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 22/03/10)

Children. After reviewing the risk of nephrogenic systemic fibrosis associated with gadolinium chelates, the EMEA's Committee for Medicinal Products for Human Use[1] (CHMP) contra-indicated the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide) in neonates. Furthermore, when medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agents (gadobutrol, gadoterate, and gadoteridol) are used in neonates, or when any gadolinium chelate is used in infants, a single lowest possible dose should be given and not repeated for at least 7 days.

1. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; 3 (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 27/04/10)

Myasthenia gravis. Acute deterioration of myasthenia gravis has been reported[1] in a patient after imaging of the brain using gadopentetate.

1. Nordenbo AM, Somnier FE. Acute deterioration of myasthenia gravis after intravenous administration of gadolinium-DTPA. *Lancet* 1992; 340: 1168.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies gadopentetic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Renal impairment. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy) is a rare condition that has been reported in patients with renal impairment. Use of gadolinium-containing contrast media appears to be a risk factor;[1-3] most cases have occurred with gadodiamide given in high doses for magnetic resonance angiography, but there have also been reports with other gadolinium-containing contrast media and with lower doses. It has been suggested that the mechanism involves release of free gadolinium ions into the tissues, and that the potential for this varies between the different gadolinium-based contrast media available, with gadodiamide and gadoversetamide more likely to do so.[4] The macrocyclic structure of gadoteridol and gadoterate was thought to be less prone to this effect, but further research is needed. A number of regulatory authorities including the FDA,[5] the MHRA,[6] Health Canada,[7] and the Therapeutic Goods Administration[8] (TGA) in Australia, advise that use of gadolinium-containing contrast media should be restricted in patients with severe renal impairment (GFR less than 30 mL/minute per 1.73 m^2). The TGA contra-indicates the use of gadodiamide, gadopentetate, and gadoversetamide in such patients, whereas the FDA and Health Canada advise that all gadolinium-containing contrast media should be avoided unless the diagnostic information is essential and cannot be obtained another way. The FDA gives a similar warning for use in patients with acute renal failure associated with hepato-renal syndrome or around the time of liver transplantation. More recently, the MHRA reported[9] that, after further review, the EMEA's Committee for Medicinal Products for Human Use (CHMP) contra-indicated the use of high-risk agents (gadodiamide, gadopentetate, and gadoversetamide) in those with severe renal impairment; furthermore, if use of a medium- (gadobenate, gadofosveset, and gadoxetate) or low-risk agent (gadobutrol, gadoterate, and gadoteridol) is necessary, a single lowest possible dose should be given and not repeated for at least 7 days (similar advice is also given for patients in the perioperative liver-transplantation period). For those with moderate impairment (GFR 30 to 59 mL/minute per 1.73 m^2), the CHMP advises that if use of a high-risk agent is necessary, a single lowest possible dose should be given and not repeated for at least 7 days. The value of haemodialysis to remove gadolinium-containing contrast media after use is unknown. The CHMP also advises that renal function should be tested in all patients receiving high-risk agents, and is generally advisa-

ble for those receiving medium- or low-risk agents, particularly patients aged 65 years or older.

1. Perazella MA, Rodby RA. Gadolinium-induced nephrogenic systemic fibrosis in patients with kidney disease. *Am J Med* 2007; **120**: 561–2.
2. Health Canada. Gadolinium-containing contrast agents and nephrogenic systemic fibrosis: update. *Can Adverse React News* 2007; **17** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v17n4-eng.pdf (accessed 25/08/10)
3. Moreno-Romero JA, *et al.* Nephrogenic systemic fibrosis: a case series suggesting gadolinium as a possible aetiological factor. *Br J Dermatol* 2007; **157**: 783–7.
4. Penfield JG, Reilly RF. Nephrogenic systemic fibrosis risk: is there a difference between gadolinium-based contrast agents? *Semin Dial* 2008; **21**: 129–34.
5. FDA. Gadolinium-containing contrast agents for magnetic resonance imaging (MRI): Omniscan, OptiMARK, Magnevist, ProHance, and MultiHance (issued 8th June 2006, updated 22nd December, 2006 and 23rd May, 2007). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142884.htm (accessed 24/08/10)
6. MHRA/CHM. Gadolinium-containing MRI contrast agents: nephrogenic systemic fibrosis. *Drug Safety Update* 2007; **1** (1): 2–3. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2031801&RevisionSelectionMethod=LatestReleased (accessed 14/07/08)
7. Health Canada. Association of nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy (NSF/NFD) with the use of gadolinium-containing contrast agents (issued 9th March, 2007). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/gadolinium_nth-aah-eng.pdf (accessed 18/03/09)
8. Adverse Drug Reactions Advisory Committee (ADRAC). MRI scans with gadolinium-containing contrast agents and the risk of nephrogenic systemic fibrosis—caution in patients with renal impairment. *Aust Adverse Drug React Bull* 2008; **27**: 2. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0802.pdf (accessed 18/03/09)
9. MHRA/CHM. Gadolinium-containing contrast agents: new advice to minimise the risk of nephrogenic systemic fibrosis. *Drug Safety Update* 2010; **3** (6): 3–5. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON068297 (accessed 22/03/10)

Pharmacokinetics

Gadopentetate is rapidly distributed into the extracellular space after intravenous injection. An elimination half-life of 1.6 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours. It does not appear to bind to plasma proteins. A small amount is distributed into breast milk. Gadopentetate is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Magnevist; Opacite; Viewgam; ***Austral.***: Magnevist; ***Austria***: Magnegita; Magnevist; ***Belg.***: Magnegita; Magnevist; ***Braz.***: Magnevistan; ***Canad.***: Magnevist; ***Chile***: Magnevistan†; ***Cz.***: Magnegita; Magnetolux; Magnevist; ***Denm.***: Magnegita†; Magnevist; Magnograf; ***Fin.***: Magnevist; ***Fr.***: Magnegita; Magnevist; ***Ger.***: Magnegita; Magnevist; MR-Lux; ***Gr.***: Magnevist; ***Hung.***: Magnevist; ***India***: Magnevist; ***Irl.***: Magnegita; Magnetolux; Magnevist; ***Israel***: Gado-MRI; Magnetol; ***Ital.***: Magnevist; ***Mex.***: Viewgam†; ***Neth.***: Magnegita; Magnevist†; Magnograf†; ***Norw.***: Magnevist; ***NZ***: Magnevist; ***Philipp.***: Gadomin; ***Port.***: Ceacont; Magnegita; Magnevist; ***Rus.***: Magnevist (Магневист); ***S.Afr.***: Magnevist; ***Spain***: Magnetolux; Magnevist; Magnograf†; ***Swed.***: Magnevist; ***Switz.***: Magnevist; Magnograf; MR-Lux; ***Turk.***: Magnevist; ***UK***: Magnevist; ***Ukr.***: Magnilek (Магнилек); Tomovist (Томовист); ***USA***: Magnevist; ***Venez.***: Magnevistan.

Pharmacopoeial Preparations
USP 36: Gadopentetate Dimeglumine Injection.

Gadoteric Acid *(BAN, rINN)*

Acide Gadotérique; Ácido gadotérico; Acidum Gadotericum; Gadoteerihappo; Gadotérico, ácido; Gadotersyra; Gd-DOTA; ZK-112004; Гадотеровая Кислота.

Hydrogen [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraaceto(4-)]gadolinate(1-); Hydrogen [1,4,7,10-tetrakis(carboxylatomethyl)-1,4,7,10-tetra-azacyclododecane-κ^4N]gadolinate (1-).

$C_{16}H_{25}GdN_4O_8$=558.6
CAS — 72573-82-1.
ATC — V08CA02.
ATC Vet — QV08CA02.
UNII — QVF9Y6955W.

Meglumine Gadoterate *(BANM, rINNM)*

Gadotérate de Méglumine; Gadoterate Meglumine (USAN); Gadoterato de meglumina; Meglumini Gadoteras; P-449; Меглумина Гадотерат.

$C_{16}H_{25}N_4O_8C_7H_{17}NO_5Gd$=753.9
CAS — 92943-93-6.
ATC — V08CA02.
ATC Vet — QV08CA02.

Uses and Administration

Gadoteric acid is an ionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body, and in magnetic resonance angiography.

Gadoteric acid is given intravenously as the meglumine salt. It is available as a solution containing meglumine gadoterate 376.9 mg/mL (0.5 mmol/mL). The usual dose in adults and children is 0.2 mL/kg (0.1 mmol/kg) by intravenous injection. A second dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given within 30 minutes if necessary. For angiography, a dose of 0.1 to 0.2 mL/kg (0.05 to 0.1 mmol/kg) may be given, repeated if required.

Administration in children. For doses of gadoteric acid in children, see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Hypersensitivity. For reports of anaphylactoid reactions with gadoterate, see under Adverse Effects of Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoterate is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. A plasma half-life of about 1.5 hours has been reported. It is not metabolised and about 90% of a dose is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Dotarem; ***Austral.***: Dotarem; ***Austria***: Artirem; Dotarem; ***Belg.***: Artirem; Dotarem; ***Chile***: Dotarem; ***Cz.***: Dotarem; ***Denm.***: Dotarem; ***Fin.***: Dotarem; ***Fr.***: Artirem; Dotarem; ***Ger.***: Artirem; Dotarem; ***Gr.***: Dotarem; ***Hung.***: Dotarem; ***Irl.***: Dotarem; ***Israel***: Dotarem; ***Ital.***: Dotarem; ***Neth.***: Artirem; Dotarem; ***Norw.***: Dotarem; ***NZ***: Dotarem; ***Port.***: Dotarem; ***Rus.***: Dotarem (Дотарем); ***Spain***: Dotarem; ***Swed.***: Dotarem; ***Switz.***: Artirem; Dotarem; ***Thai.***: Dotarem; ***Turk.***: Dotarem; ***USA***: Dotarem; ***Venez.***: Dotarem.

Gadoteridol *(BAN, USAN, rINN)*

Gadotéridol; Gadoteridoli; Gadoteridolum; Gd-HP-DO3A; SQ-32692; Гадотеридол.

(±)-[10-(2-Hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)]gadolinium.

$C_{17}H_{29}GdN_4O_7$=558.7
CAS — 120066-54-8.
ATC — V08CA04.
ATC Vet — QV08CA04.
UNII — 0199MV609F.

Pharmacopoeias. In *US.*

USP 36: (Gadoteridol). A white to off-white, odourless, crystalline powder. Freely soluble in water and in methyl alcohol; soluble in isopropyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Gadoteridol is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body.

Gadoteridol is available as a solution containing 279.3 mg/mL (0.5 mmol/mL). The usual adult dose is 0.2 mL/kg (0.1 mmol/kg) intravenously; for CNS imaging, an additional dose of up to 0.4 mL/kg (0.2 mmol/kg) may be given up to 30 minutes after the first if necessary. A single dose of 0.2 mL/kg (0.1 mmol/kg) is used in children from 6 months of age (see also below).

Administration in children. In some countries, gadoteridol is licensed for use in children from 6 months of age; UK licensed product information notes that experience is limited in children between 6 months and 2 years of age, and advises particular caution if it is to be used in this age group. US licensed product information considers that safety and efficacy have not been demonstrated in this age group, and only indicates the product for imaging cranial and spinal structures in those aged 2 years and over. For doses see Uses and Administration, above.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2 and p. 1586.2, respectively.

Reviews.

1. Runge VM, Parker JR. Worldwide clinical safety assessment of gadoteridol injection: an update. *Eur Radiol* 1997; **7** (suppl 5): 243–5.

Hypersensitivity. For a report of an anaphylactoid reaction with gadoteridol, see under Adverse Effects of Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoteridol is distributed into extracellular fluid after intravenous injection. About 94% of a dose is excreted unchanged in the urine within 24 hours. An elimination half-life of about 1.57 hours has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Prohance; ***Austria***: Prohance; ***Belg.***: Prohance; ***Canad.***: ProHance; ***Cz.***: Prohance; ***Denm.***: Prohance; ***Fin.***: Prohance; ***Fr.***: Prohance; ***Ger.***: Prohance; ***Irl.***: Prohance; ***Ital.***: Prohance; ***Jpn***: Prohance; ***Neth.***: Prohance; ***Norw.***: Prohance; ***Spain***: Prohance; ***Swed.***: Prohance; ***Switz.***: Prohance; ***UK***: Prohance; ***USA***: Prohance.

Pharmacopoeial Preparations
USP 36: Gadoteridol Injection.

Gadoversetamide *(BAN, USAN, rINN)*

Gadoversetamida; Gadoversétamide; Gadoversetamidum; MP-L177; Гадоверсетамид.

N,N-Bis[2-[[(carboxymethyl)[(2-methoxyethyl)carbamoyl]methyl]amino]ethyl]glycinato(3-)]gadolinium.

$C_{20}H_{34}GdN_5O_{10}$=661.8
CAS — 131069-91-5.
ATC — V08CA06.
ATC Vet — QV08CA06.
UNII — RLM74T3Z9D.

Pharmacopoeias. In *US.*

USP 36: (Gadoversetamide). A white odourless powder. Freely soluble in water. Store in airtight containers. Protect from light.

Uses and Administration

Gadoversetamide is a nonionic gadolinium chelate with actions and uses similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It distributes mainly into extracellular fluid, but does not cross the blood-brain barrier, and is used in imaging of cranial and spinal structures and of the whole body (particularly to visualise the liver).

Gadoversetamide is available as a solution containing 330.9 mg/mL (0.5 mmol/mL). The usual dose is 0.2 mL/kg (0.1 mmol/kg) intravenously.

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Interference with diagnostic tests. Like gadodiamide (see p. 1585.3), gadoversetamide may interfere with colorimetric methods for measuring serum-calcium concentrations.

Gadoversetamide may also interfere with measurement of serum-copper, iron, and zinc concentrations.

Renal impairment. For the view that gadoversetamide may carry an increased risk of the development of nephrogenic systemic fibrosis in patients with renal impairment, see p. 1586.3.

Pharmacokinetics

Gadoversetamide is distributed into the extracellular space after intravenous injection. It is not bound to plasma proteins. An elimination half-life of about 1.7 hours has been reported. It is not metabolised and about 95.5% of a dose is excreted in the urine within 24 hours. Gadoversetamide is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optimark; ***Austral.***: Optimark; ***Austria***: Optimark; ***Belg.***: Optimark; ***Canad.***: Optimark; ***Cz.***: Optimark; ***Denm.***: Optimark†; ***Gr.***: Optimark; ***Hung.***: Optimark; ***Irl.***: Optimark; ***Neth.***: Optimark; ***Norw.***: Optimark; ***Pol.***:

Optimark; *Port.*: Optimark; *Rus.*: Optimark (Оптимарк); *Spain*: Optimark; *Swed.*: Optimark; *USA*: Optimark.

Pharmacopoeial Preparations
USP 36: Gadoversetamide Injection.

Gadoxetic Acid *(rINN)*

Acide Gadoxétique; Ácido gadoxético; Acidum Gadoxeticum; Gadoxético, ácido; Gd-EOB-DTPA; Гадоксетовая Кислота.

Dihydrogen [*N*-[(2*S*)-2-[bis(carboxymethyl)amino]-3-(*p*-ethoxyphenyl)propyl]-*N*-[2-[bis(carboxymethyl)amino]ethyl]glycinato(5-)]gadolinate(2-).

$C_{23}H_{30}GdN_3O_{11}$=681.8.

CAS — 135326-11-3 (gadoxetic acid).

ATC — V08CA10.

ATC Vet — QV08CA10.

UNII — 3QJA87N40S.

Sodium Gadoxetate *(rINNM)*

Gadoxétate de Sodium; Gadoxetate Disodium (USAN); Gadoxetate Sodium; Gadoxetato de sodio; Natrii Gadoxetas; ZK-139834; Натрий Гадоксетат.

$C_{23}H_{28}GdN_3Na_2O_{11}$=725.7

CAS — 135326-22-6.

ATC — V08CA10.

ATC Vet — QV08CA10.

UNII — HOY74VZE0M.

Uses and Administration

Gadoxetic acid is an ionic gadolinium chelate with actions similar to those of gadopentetic acid (p. 1586.1). It has paramagnetic properties and is used as a magnetic resonance contrast medium (p. 1580.1). It is taken up by the liver and excreted in bile and is used in imaging of the liver.

Gadoxetic acid is given intravenously as the sodium salt. It is available as a solution containing sodium gadoxetate 181.4 mg/mL (0.25 mmol/mL). The usual dose is 0.1 mL/kg (0.025 mmol/kg).

Adverse Effects and Precautions

As for Gadopentetic Acid, p. 1586.2.

Pharmacokinetics

Gadoxetate is distributed into the extracellular space after intravenous injection and is also taken up by the liver. It is less than 10% bound to plasma proteins. It is excreted in about equal amounts in the bile and in the urine. An elimination half-life of about 1 hour has been reported. Gadoxetate is removed by haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Primovist; *Austria*: Primovist; *Belg.*: Primovist; *Canad.*: Primovist; *China*: Primovist (普美显); *Cz.*: Primovist; *Fin.*: Primovist; *Ger.*: Primovist; *Gr.*: Primovist; *Hung.*: Primovist; *Irl.*: Primovist; *Ital.*: Primovist; *Neth.*: Primovist; *Norw.*: Primovist; *Port.*: Primovist; *Rus.*: Primovist (Примовист); *Spain*: Primovist; *Swed.*: Primovist; *Switz.*: Primovist; *Turk.*: Primovist; *UK*: Primovist; *USA*: Eovist.

Galactose *(USAN)*

D-Galactopyranose; α-D-Galactopyranose; Galactosa; D-Galactose; Galactosum; Galaktoosi; Galaktos; Galaktosa; Galaktoze; Galaktóz; Galaktoza; Галактоза.

$C_6H_{12}O_6$=180.2.

CAS — 59-23-4 (D-galactose); 3646-73-9 (α-D-galactose).

ATC — V04CE01; V08DA02 (microparticles of galactose).

ATC Vet — QV04CE01; QV08DA02 (microparticles of galactose).

UNII — X2RN3Q8DNE.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Galactose). A white or almost white, crystalline or finely granulated powder. Freely soluble or soluble in water; very slightly soluble in alcohol.

USNF 31: (Galactose). A white, crystalline or finely granulated powder. Soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Profile

Galactose is a naturally occurring monosaccharide used as an ultrasound contrast medium (p. 1580.2); dissolution of galactose microparticles releases microbubbles of air that provide echo-enhancement.

Galactose may be given as a microbubble-microparticle suspension prepared immediately before use by suspending 3 g of galactose microparticles in 13.5 mL of a solution containing 200 mg/mL galactose. When given transcervically to enhance ultrasound imaging of the female genital tract, the usual dose is 2 to 5 mL, with additional doses of 1 to 2 mL as required, to a maximum of 30 mL. When given intravenously in echocardiography, the usual dose is 4 to 10 mL; infants and children may be given the following doses according to age: neonates to 4 weeks, 0.5 mL; 4 weeks to 12 months, 1 to 2 mL; 1 to 5 years, 2 mL. Adults and children, including infants, may be given the maximum of 5 injections.

Similar suspensions of galactose, with palmitic acid to stabilise the microbubbles, prepared immediately before use by suspending galactose microparticles in water for injection to concentrations of 200, 300, and 400 mg/mL are also used. When given intravenously to enhance ultrasound imaging of blood vessels and in echocardiography, the dose and strength used varies depending on the procedure. When given as a bladder instillation for diagnosis of vesicoureteral reflux in children, the 300 mg/mL suspension is recommended; the volume used in infants is 5 mL and in older children 10% of the measured bladder volume.

The clearance of galactose given intravenously has been used as a measure of liver function. Galactose labelled with carbon-13 (p. 2470.3) has also been used.

Administration in children. Galactose is licensed for use in infants and children in echocardiography and for diagnosis of vesicoureteral reflux. For doses, see Uses and Administration, above.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies galactose as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Precautions. Preparations that contain, or are metabolised to, galactose may interfere with the results from glucose tests (p. 2516.3). Overestimation of glucose results may mask hypoglycaemia, resulting in the inappropriate use of insulin.[1,2] Licensed product information warns that galactose should not be used for visualisation in patients with galactosaemia.

1. MHRA Medical device alert: ref MDA/2007/058 issued 19th July, 2007. Available at: http://www.mhra.gov.uk/PrintPreview/PublicationSP/CON2031807 (accessed 01/07/08)
2. FDA. Important safety information on interference with blood glucose measurement following use of parenteral maltose/parenteral galactose/oral xylose-containing products (issued November 2005). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm154213.htm (accessed 24/08/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Levovist; *Austria*: Echovist; *Fr.*: Echovist†; Levovist†; *Ger.*: Echovist; Levovist†; *Gr.*: L-Vist; Levovist; *Hung.*: Echovist†; *Israel*: Echovist; *Ital.*: Levovist; *NZ*: Levovist†; *Spain*: Levovist†; *Swed.*: Echovist†; *Switz.*: Levovist†; *UK*: Echovist†.

Multi-ingredient Preparations. *India*: Osmowin; *Ital.*: Reumilase.

Iobitridol *(BAN, rINN)*

Iobitridolum; Jobitridol; Jobitridoli; Йобитридол.

N,N'-Bis(2,3-dihydroxypropyl)-5-[2-(hydroxymethyl)hydracrylamido]-2,4,6-triiodo-*N,N'*-dimethylisophthalamide.

$C_{20}H_{28}I_3N_3O_9$=835.2

CAS — 136949-58-1.

ATC — V08AB11.

ATC Vet — QV08AB11.

UNII — 182ECH14UH.

Profile

Iobitridol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, or by instillation into body cavities and is used in a wide range of procedures including angiography, arthrography, cholangiopancreatography, and hysterosalpingography. It is also used for contrast enhancement in computed tomography.

It is usually available as solutions containing 54.84 to 76.78% of iobitridol (equivalent to 250 to 350 mg/mL of iodine). The dose and strength used varies depending on the procedure and route.

References.
1. Petersein J, *et al.* Results of the safety and efficacy of iobitridol in more than 61,000 patients. *Eur Radiol* 2003; 13: 2006–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iobitridol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Xenetic†; Xenetix; *Austria*: Xenetix; *Belg.*: Xenetix; *Chile*: Xenetix; *Cz.*: Xenetix; *Denm.*: Xenetix; *Fin.*: Xenetix; *Fr.*: Xenetix; *Ger.*: Xenetix; *Gr.*: Xenetix; *Hung.*: Xenetix; *Irl.*: Xenetix; *Israel*: Xenetix; *Ital.*: Xenetix; *Neth.*: Xenetix; *Norw.*: Xenetix; *Port.*: Xenetix; *Rus.*: Xenetix (Ксенетикс); *Spain*: Xenetix; *Swed.*: Xenetix; *Switz.*: Xenetix; *Thai.*: Xenetix; *Turk.*: Xenetix; *Venez.*: Xenetix.

Iocetamic Acid *(BAN, USAN, pINN)*

Acide Iocétamique; Ácido iocetámico; Acidum Iocetamicum; DRC-1201; Iocetámico, ácido; Jocetamsyra; Josetaamihappo; MP-620; Йоцетамовая Кислота.

N-Acetyl-*N*-(3-amino-2,4,6-tri-iodophenyl)-2-methyl-β-alanine; 2-[*N*-(3-Amino-2,4,6-tri-iodophenyl)acetamidomethyl]-propionic acid.

$C_{12}H_{13}I_3N_2O_3$=614.0

CAS — 16034-77-8.

ATC — V08AC07.

ATC Vet — QV08AC07.

UNII — FA675Q0E3E.

Description. Iocetamic acid contains about 62% of I.

Profile

Iocetamic acid is an ionic monomeric iodinated radiographic contrast medium with similar properties to iopanoic acid (p. 1591.1). It is absorbed from the gastrointestinal tract and excreted in bile and has been given orally for cholecystography.

Iodamide *(BAN, USAN, rINN)*

Ametriodinic Acid; B-4130; Iodamida; Iodamidum; Jodamid; Jodiamidi; SH-926; Йодамид.

α,5-Diacetamido-2,4,6-tri-iodo-*m*-toluic acid; 3-Acetamido-5-acetamidomethyl-2,4,6-tri-iodobenzoic acid.

$C_{12}H_{11}I_3N_2O_4$=627.9

CAS — 440-58-4.

ATC — V08AA03.

ATC Vet — QV08AA03.

UNII — 4RII332O0R.

Description. Iodamide contains about 60.6% of I.

Pharmacopoeias. In *Jpn.*

Meglumine Iodamide *(BANM, rINNM)*

Iodamida de meglumina; Iodamide Meglumine (USAN); Iodamide Méglumine; Meglumini Iodamidum; Меглумина Йодамид.

The *N*-methylglucamine salt of iodamide.

$C_{12}H_{11}I_3N_2O_4.C_7H_{17}NO_5$=823.2

CAS — 18656-21-8.

ATC — V08AA03.

ATC Vet — QV08AA03.

UNII — 6X283535A3.

Description. Meglumine iodamide contains about 46.3% of I.

Sodium Iodamide *(BANM, rINNM)*

Iodamida sódica; Iodamide Sodique; Iodamide Sodium; Natrii Iodamidum; Натрий Йодамид.

$C_{12}H_{10}I_3N_2NaO_4$=649.9

CAS — 10098-82-5.

ATC — V08AA03.

ATC Vet — QV08AA03.

Description. Sodium iodamide contains about 58.6% of I.

Profile

Iodamide is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It is used in many procedures and may be given intravenously or by other routes, for example by instillation into the bladder or uterus; it has also been used for computed tomography.

It has been given as a 24 to 65% solution of the meglumine salt or as a mixture of the sodium and meglumine salts; solutions of the sodium salt have also been used. The dose varies according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Uromiro; *Venez.*: Uromiron.

Iodised Oil

Aceite yodado; Ethiodized Oil; Этиловые Эфиры Йодированных Жирных Кислот.

CAS — 8001-40-9 (iodised oil); 8008-53-5 (ethiodized oil injection).
ATC — V08AD01.
ATC Vet — QV08AD01.
UNII — KZW0R0686Q.

Description. Iodised oil is an iodine addition product of the ethyl esters of the fatty acids obtained from poppy-seed oil. It contains about 35 to 39% of combined iodine.

Incompatibility. Because of its solvent action on polystyrene, iodised oil injection should not be given in syringes made with polystyrene.

Uses and Administration

Iodised oil is an iodinated radiographic contrast medium (p. 1580.1) that is used mainly for lymphography. It has been used for hysterosalpingography but water-soluble agents are preferred. Although some preparations have been used in bronchography, the fluid injection of iodised oil is unsuitable for such use. Doses are dependent upon the procedure.

Because it is slowly metabolised to release iodine, iodised oil is used in the management of iodine deficiency (p. 2337.3).

Infertility. For reference to the use of iodised oil in the management of infertility, see Hysterosalpingography under Adverse Effects and Precautions, below.

Malignant neoplasms. Intra-arterial injection of iodised oil has been used in both the diagnosis and management of malignant neoplasms of the liver (p. 709.3). After injection into the hepatic artery, iodised oil is selectively retained by hepatic carcinomas and may have a role as an adjunct to computed tomography for both diagnosis and monitoring.[1-3] It has also been used in the management of hepatic carcinoma,[2,4] either to increase the retention of antineoplastics (chemoembolisation),[5] or to provide targeted delivery of radioactive iodine.[6]

1. Dalla Palma L. Diagnostic imaging and interventional therapy of hepatocellular carcinoma. *Br J Radiol* 1998; 71: 808–18.
2. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003; 52 (suppl): iii1–iii8. Also available at: http://www.bsg.org.uk/pdf_word_docs/hcc.pdf (accessed 27/03/06)
3. Zheng X-H, *et al.* Detection of hypervascular hepatocellular carcinoma: comparison of multi-detector CT with digital subtraction angiography and Lipiodol CT. *World J Gastroenterol* 2005; 11: 200–203.
4. Trinchet JC, *et al.* Review article: intra-arterial treatments in patients with hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003; 17 (suppl 2): 111–18.
5. Group d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995; 332: 1256–61.
6. Lau WY, *et al.* Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999; 353: 797–801.

Adverse Effects and Precautions

The risk of hypersensitivity reactions or iodism is greater after the use of iodised oil than after water-soluble iodinated contrast media such as the amidotrizoates. Pulmonary oil embolism is reported to be relatively frequent after lymphography but is not usually severe; however, hypotension, tachycardia, and pulmonary oedema and infarction may occur rarely and deaths have been reported in patients with pulmonary disease. Chemical pneumonitis, oedema, granuloma formation, and goitre have occurred.

Great care must be taken to avoid vascular structures, because of the danger of oil embolism; it should therefore not be used in areas affected by haemorrhage or local trauma. Iodised oil should be used with care in patients with thyroid dysfunction or a history of allergic reactions. Use may interfere with thyroid-function tests for several months.

Hysterosalpingography. The use of oily contrast media such as iodised oil for hysterosalpingography has been associated with serious adverse effects, including tubal occlusion,[1] and cerebral and pulmonary oil embolism,[2,3] and water-soluble contrast media are usually preferred. However, diagnostic hysterosalpingography using iodised oil has been associated with an increase in fertility[4] and randomised trials[5,6] using iodised oil for treatment in patients with unexplained infertility have found a similar effect.

1. Wright FW, Stallworthy J. Female sterility produced by investigation. *BMJ* 1973; 3: 632.
2. Dan U, *et al.* Cerebral embolization and coma after hysterosalpingography with oil-soluble contrast medium. *Fertil Steril* 1990; 53: 939–40.
3. Uzun O, *et al.* Pulmonary and cerebral oil embolism after hysterosalpingography with oil soluble contrast medium. *Respirology* 2004; 9: 134–6.
4. Johnson NP. A review of the use of lipiodol flushing for unexplained infertility. *Treat Endocrinol* 2005; 4: 233–43.
5. Nugent D, *et al.* A randomized controlled trial of tubal flushing with lipiodol for unexplained infertility. *Fertil Steril* 2002; 77: 173–5.
6. Johnson NP, *et al.* The FLUSH trial—flushing with lipiodol for unexplained (and endometriosis-related) subfertility by hysterosalpingography: a randomized trial. *Hum Reprod* 2004; 19: 2043–51.

Pharmacokinetics

Iodised oil may persist in the body for several weeks or months. It is only slowly absorbed from most body sites, although absorption from the peritoneal cavity is stated to be relatively rapid. It is reported to be slowly metabolised to fatty acids and iodine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lipiodol; *Austral.*: Lipiodol; *Austria*: Lipiodol; *Belg.*: Lipiodol; *Canad.*: Lipiodol; *Chile*: Lipiodol; *Cz.*: Lipiodol; *Denm.*: Lipiodol; *Fr.*: Lipiodol; *Ger.*: Lipiodol; *Gr.*: Lipiodol; *Hung.*: Lipiodol; *Irl.*: Lipiodol; *Israel*: Lipiodol; *Ital.*: Lipiodol; *Neth.*: Lipiodol; *NZ*: Lipiodol; *Port.*: Lipiodol; *Switz.*: Lipiodol; *Thai.*: Lipiodol Ultra-Fluide; *Turk.*: Lipiodol; *UK*: Lipiodol; *USA*: Ethiodol†; *Venez.*: Lipiodol.

Pharmacopoeial Preparations
BP 2014: Iodised Oil Fluid Injection;
USP 36: Ethiodized Oil Injection.

Iodixanol *(BAN, USAN, rINN)*

2-5410-3A; Iodixanolum; Jodiksanoli; Jodixanol; Йодиксанол.

5,5′-[(2-Hydroxytrimethylene)bis(acetylimino)]bis[*N*,*N*′-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide].

$C_{35}H_{44}I_6N_6O_{15}$=1550.2
CAS — 92339-11-2.
ATC — V08AB09.
ATC Vet — QV08AB09.
UNII — HW8W27HTXX.

Description. Iodixanol contains about 49.1% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Iodixanol). A white or almost white, hygroscopic powder. Freely soluble in water; sparingly soluble in methyl alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Iodixanol). A white to off-white, amorphous, odourless, hygroscopic powder. Freely soluble in water. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iodixanol is a nonionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is iso-osmolar with blood. It may be given intravenously, intra-arterially, intrathecally, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, cholangiopancreatography, hysterosalpingography, myelography, and urography, as well as for imaging of the upper gastrointestinal tract and for contrast enhancement during computed tomography.

Iodixanol is usually available as a solution containing between 30.5 and 65.2% of iodixanol (equivalent to between 150 and 320 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

References.
1. Spencer CM, Goa KL. Iodixanol: a review of its pharmacodynamic and pharmacokinetic properties and diagnostic use as an x-ray contrast medium. *Drugs* 1996; 52: 899–927.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. For adverse effects relating to the use of nonionic contrast media such as iodixanol for myelography, see under Iohexol (p. 1590.2).

References.
1. McCullough PA. Renal safety of iodixanol. *Expert Rev Cardiovasc Ther* 2006; 4: 655–61.
2. Heinrich MC, *et al.* Nephrotoxicity of iso-osmolar iodixanol compared with nonionic low-osmolar contrast media: meta-analysis of randomized controlled trials. *Radiology* 2009; 250: 68–86.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iodixanol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

Iodixanol is rapidly distributed into extracellular fluid after intravenous injection. It is not bound to plasma proteins. It is not metabolised and about 97% of a dose is excreted in the urine within 24 hours. A terminal elimination half-life of about 2 hours has been reported. Iodixanol is removed by dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Visipaque; *Austral.*: Visipaque; *Austria*: Visipaque; *Belg.*: Visipaque; *Canad.*: Visipaque; *Chile*: Visipaque; *China*: Visipaque (威视派克); *Cz.*: Visipaque; *Denm.*: Visipaque; *Fin.*: Visipaque; *Fr.*: Visipaque; *Ger.*: Visipaque; *Gr.*: Visipaque; *Hung.*: Visipaque; *Irl.*: Visipaque; *Israel*: Visipaque; *Ital.*: Visipaque; *Neth.*: Visipaque; *Norw.*: Visipaque; *NZ*: Visipaque; *Port.*: Visipaque; *Rus.*: Visipaque (Визипак); *Spain*: Visipaque; *Swed.*: Visipaque; *Switz.*: Visipaque; *Turk.*: Visipaque; *UK*: Visipaque; *Ukr.*: Visipaque (Визипак); *USA*: Visipaque.

Pharmacopoeial Preparations
USP 36: Iodixanol Injection.

Iodoxamic Acid *(BAN, USAN, rINN)*

Acide Iodoxamique; Ácido Iodoxámico; Acidum Iodoxamicum; B-10610; Iodoxámico, ácido; Jodoksaamihappo; Jodoxamsyra; SQ-21982; Йодоксамовая Кислота.

3,3′-(4,7,10,13-Tetraoxahexadecanedioyldiamino)bis(2,4,6-tri-iodobenzoic acid).
$C_{36}H_{36}I_6N_2O_{16}$=1287.9
CAS — 31127-82-9.
ATC — V08AC01.
ATC Vet — QV08AC01.
UNII — NS1Y283HW4.

Description. Iodoxamic acid contains about 59.1% of I.

Meglumine Iodoxamate *(BANM, rINNM)*

Dimeglumine Iodoxamate; Iodoxamate de Méglumine; Iodoxamate Meglumine (USAN); Iodoxamato de meglumina; Meglumini Iodoxamas; Меглумина Йодоксамат.

The di(*N*-methylglucamine) salt of iodoxamic acid.
$C_{26}H_{26}I_6N_2O_{16}(C_7H_{17}NO_5)_2$=1678.4
CAS — 51764-33-1.
ATC — V08AC01.
ATC Vet — QV08AC01.
UNII — CIX5G6J9R1.

Description. Meglumine iodoxamate contains about 45.4% of I.

Profile

Iodoxamic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1) that has been used intravenously as the meglumine salt for cholecystography and cholangiography.

Iofendylate *(BAN, rINN)*

Ethyl Iodophenylundecylate; Iodophendylate; Iofendilato; Iofendylatum; Iophendylate; Jofendylaatti; Jofendylat; Йофендилат.

A mixture of stereoisomers of ethyl 10-(4-iodophenyl) undecanoate.
$C_{19}H_{29}IO_2$=416.3
CAS — 99-79-6; 1320-11-2.
ATC — V08AD04.
ATC Vet — QV08AD04.
UNII — 2990I809YI (iophendylate); 6V3I57K9UL (ethyl 10-(4-iodophenyl)undecanoate).

Description. Iofendylate contains about 30.5% of I.

Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Iophendylate). A colourless to pale yellow, viscous liquid, darkening on long exposure to air. Is odourless or has a faintly ethereal odour. Very slightly soluble in water; freely soluble in alcohol, in chloroform, in ether, and in benzene. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Iofendylate is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It was formerly used for

myelography, but was associated with serious adverse effects, including allergy, arachnoiditis, and aseptic meningitis, and has now been superseded by nonionic media. Residues of iofendylate remaining years after myelography have been associated with adverse effects. Other former uses included ventriculography, and visualisation of the fetus in the amniotic sac.

Preparations

Pharmacopoeial Preparations
BP 2014: Iofendylate Injection;
USP 36: Iophendylate Injection.

Ioglicic Acid *(BAN, USAN, rINN)*

Acide Ioglicique; Ácido Ioglícico; Acidum Ioglicicum; Ioglícico, ácido; Joglicinsyra; Joglisiinihappo; SH-H-200-AB; Йоглициевая Кислота.
5-Acetamido-2,4,6-tri-iodo-*N*-(methylcarbamoylmethyl)isophthalamic acid.
$C_{13}H_{12}I_3N_3O_5$=671.0
CAS — 49755-67-1.
ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — 3LGR5S8101.

Description. Ioglicic acid contains about 56.7% of I.

Meglumine Ioglicate *(BANM, rINNM)*

Ioglicate de Méglumine; Ioglicate Meglumine; Ioglicato de meglumina; Meglumini Ioglicas; Меглумина Йоглицинат.
The *N*-methylglucamine salt of ioglicic acid.
$C_{13}H_{12}I_3N_3O_5.C_7H_{17}NO_5$=866.2
ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — FK97TOF9G0.

Description. Meglumine ioglicate contains about 44.0% of I.

Sodium Ioglicate *(BANM, rINNM)*

Ioglicate de Sodium; Ioglicate Sodium; Ioglicato sódico; Natrii Ioglicas; Натрий Йоглицинат.
$C_{13}H_{11}I_3N_3NaO_5$=693.0
ATC — V08AA06.
ATC Vet — QV08AA06.
UNII — YS85R4Y0EA.

Description. Sodium ioglicate contains about 54.9% of I.

Profile

Ioglicic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) that has been used, as the meglumine and sodium salts, for diagnostic procedures.

Iohexol *(BAN, USAN, rINN)*

Iohexolum; Joheksoli; Joheksolis; Johexol; Win-39424; Йогексол.
N,N'-Bis(2,3-dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.
$C_{19}H_{26}I_3N_3O_9$=821.1
CAS — 66108-95-0.
ATC — V08AB02.
ATC Vet — QV08AB02.
UNII — 4419T9MX03.

Description. Iohexol contains about 46.4% of I.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Iohexol). A white or greyish-white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; freely soluble in methyl alcohol. Store in airtight containers. Protect from light.

USP 36: (Iohexol). A white to off-white, hygroscopic, odourless powder. Very soluble in water and in methyl alcohol; practically insoluble or insoluble in chloroform and in ether. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iohexol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, orally, rectally, or by instillation into body cavities and is used in diagnostic procedures including myelography, angiography, urography, arthrography, and visualisation of the gastrointestinal tract and body cavities. Iohexol is also used to produce contrast enhancement during computed tomography.

Iohexol is usually available as solutions containing 30.2 to 75.5% of iohexol (equivalent to 140 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

Adverse Effects, Treatment, and Precautions

Iohexol and other nonionic iodinated contrast media have similar adverse effects and precautions to ionic media but the effects tend to be less severe and the incidence is generally lower; see under the amidotrizoates, p. 1582.1 and p. 1583.1 for details.

Additional neurological adverse effects may occur when nonionic media such as iohexol are used for myelography. These include severe headache, backache, neck stiffness, dizziness, and leg or sciatic-type pain. Convulsions, aseptic meningitis, and mild and transitory perceptual aberrations, such as visual and speech disturbances, and confusion, may occur occasionally; rarely, more severe mental disturbances have occurred. Urinary retention has also been reported.

Breast feeding. Iohexol is distributed into breast milk in very small quantities[1] but no adverse effects have been seen in breast-feeding infants whose mothers were receiving iohexol and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Nielsen ST, *et al.* Excretion of iohexol and metrizoate in human breast milk. *Acta Radiol* 1987; **28**: 523–6.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Effects on the nervous system. Encephalopathy developed in a 48-year-old man with sciatica within 9 hours of iohexol for lumbar myelography but had largely resolved 48 hours after the myelogram; complete resolution took 4 days.[1] However, recovery was slow in a patient who developed paraplegia and areflexia in the legs after a similar procedure. Five months later the patient still complained of paraesthesia in her legs and could not stand without support.[2] Encephalopathy has also been reported in association with use of iohexol for coronary angiography.[3]

1. Donaghy M, *et al.* Encephalopathy after iohexol myelography. *Lancet* 1985; **ii**: 887.
2. Noda K, *et al.* Prolonged paraplegia after iohexol myelography. *Lancet* 1991; **337**: 681.
3. Sawaya RA, *et al.* Contrast-induced encephalopathy following coronary angioplasty with iohexol. *South Med J* 2007; **100**: 1054–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iohexol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Interactions

Antiarrhythmics. A small retrospective study[1] found that concurrent use of iohexol and *amiodarone* resulted in significant prolongation of the QT_c interval compared with iohexol alone. Caution was advised in the use of iohexol in patients taking antiarrhythmics that prolong QT interval.

1. Goernig M, *et al.* Iohexol contrast medium induces QT prolongation in amiodarone patients. *Br J Clin Pharmacol* 2004; **58**: 96–8.

Pharmacokinetics

After intravascular use, 90% or more of a dose of iohexol is eliminated unchanged in the urine within 24 hours. An elimination half-life of about 2 hours in patients with normal renal function has been reported. Protein binding in blood is reported to be very low.

Pregnancy. Contrast material was detected[1] in the intestines of twin neonates who were born 17 hours after iohexol was given to their mother for angiography, suggesting that transplacental transfer had taken place.

1. Moon AJ, *et al.* Transplacental passage of iohexol. *J Pediatr* 2000; **136**: 548–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Omnipaque; *Austral.*: Omnipaque; *Austria*: Accupaque; Omnipaque; *Belg.*: Omnipaque; *Canad.*: Omnipaque; *Chile*: Omnipaque; *China*: Omnipaque (欧乃派克); Ou Su (欧苏); Shuang Bei (双北); *Cz.*: Omnipaque; *Denm.*: Omnipaque; *Fin.*: Omnipaque; *Fr.*: Omnipaque; *Ger.*: Accupaque; Iohexagita; Omnipaque; *Gr.*: Accupaque; Omnipaque; *Hung.*: Omnipaque; *India*: Radiopaque; *Irl.*: Omnipaque; *Israel*: Omnipaque; *Ital.*: Omnipaque; *Neth.*: Omnipaque; *Norw.*: Omnipaque; *NZ*: Omnipaque; *Port.*: Omnipaque; *Rus.*: Omnipaque (Омнипак); Unihexol (Юнигексол); *Spain*: Nitigraf; Omnipaque; Omnitrast†; *Swed.*: Omnipaque; *Switz.*: Accupaque; Omnipaque†; *Thai.*: Iobrix; *Turk.*: Kopaq; Omnipaque; *UK*: Omnipaque; *Ukr.*: Omnipaque (Омнипак); Tomohexol (Томогексол); Unipak (Юнипак); *USA*: Omnipaque.

Pharmacopoeial Preparations
USP 36: Iohexol Injection.

Iomeprol *(BAN, USAN, rINN)*

Ioméprol; Iomeprolum; Jomeprol; Jomeproli; Йомепрол.
N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-triiodo-5-(*N*-methylglycolamido)-isophthalamide.
$C_{17}H_{22}I_3N_3O_8$=777.1
CAS — 78649-41-9.
ATC — V08AB10.
ATC Vet — QV08AB10.
UNII — 17E17JBP8L.

Description. Iomeprol contains about 49% of I.

Uses and Administration

Iomeprol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, or by instillation into body cavities, and is used in radiographic procedures including myelography, angiography, urography, and arthrography. It is also used to produce contrast enhancement during computed tomography.

Iomeprol is usually available as solutions containing 30.62 to 81.65% of iomeprol (equivalent to 150 to 400 mg/mL of iodine) and the dose and strength used vary according to the procedure and the route.

Reviews.
1. Dooley M, Jarvis B. Iomeprol: a review of its use as a contrast medium. *Drugs* 2000; **59**: 1169–86.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For adverse effects relating to the use of nonionic contrast media such as iomeprol for myelography, see under Iohexol (above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iomeprol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

After intravascular use, iomeprol is rapidly eliminated unchanged in the urine, with a terminal elimination half-life of 1.9 hours. It is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Iomeron; *Austria*: Iomeron; *Belg.*: Iomeron; *China*: Iomeron (典迈伦); *Cz.*: Iomeron; *Denm.*: Iomeron; *Fin.*: Iomeron; *Fr.*: Iomeron; *Ger.*: Imeron; *Gr.*: Iomeron; *Hong Kong*: Iomeron†; *Hung.*: Iomeron; *Irl.*: Iomeron; *Israel*: Iomeron; *Ital.*: Iomeron; *Jpn*: Iomeron; *Neth.*: Iomeron; *Norw.*: Iomeron; *NZ*: Iomeron; *Port.*: Iomeron; *Spain*: Iomeron; *Swed.*: Iomeron; *Switz.*: Iomeron; *Turk.*: Iomeron; *UK*: Iomeron.

Iopamidol *(BAN, USAN, rINN)*

B-15000; Iopamidolum; Jopamidol; Jopamidoli; Jopamidolis; SQ-13396; Йопамидол.
(*S*)-*N,N'*-Bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodo-5-lactamidoisophthalamide.
$C_{17}H_{22}I_3N_3O_8$=777.1
CAS — 60166-93-0; 62883-00-5.
ATC — V08AB04.
ATC Vet — QV08AB04.
UNII — JR13W81H44.

Description. Iopamidol contains about 49% of I.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Iopamidol). A white or almost white powder. Freely soluble in water; practically insoluble in alcohol and in dichloromethane; very slightly soluble in methyl alcohol. Protect from light.

USP 36: (Iopamidol). A white to off-white, practically odourless, powder. Very soluble in water; practically insoluble in alcohol and in chloroform; sparingly soluble in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Iopamidol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, intrathecally, intra-articularly, orally, or rectally and is used in radiographic procedures including angiography, arthrography, myelography, urography, and imaging of the gastrointestinal tract. Iopamidol is also used for contrast enhancement during computed tomography.

Iopamidol is usually available as solutions containing 30.62 to 75.5% of iopamidol (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Gastrointestinal obstruction. Enemas of iopamidol were considered safe and effective in the management of meconium ileus in extremely low-birth-weight infants.[1]

1. Nakaoka T, *et al.* Iopamidol enema treatment for meconium obstruction of prematurity in extremely low-birth weight infants: a safe and effective method. *Pediatr Surg Int* 2009; **25**: 273–6.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For the adverse effects relating to the use of nonionic contrast media such as iopamidol for myelography, see under Iohexol, p. 1590.2; for specific references, see below.

Effects on the nervous system. Reports[1-6] of serious neurological sequelae to lumbar myelography with iopamidol.

1. Wallers K, *et al.* Severe meningeal irritation after intrathecal injection of iopamidol. *BMJ* 1985; **291**: 1688.
2. Robinson C, Fon G. Adverse reaction to iopamidol. *Med J Aust* 1986; **144**: 553.
3. Bell JA, McIlwaine GG. Postmyelographic lateral rectus palsy associated with iopamidol. *BMJ* 1990; **300**: 1343–4.
4. Mallat Z, *et al.* Aseptic meningoencephalitis after iopamidol myelography. *Lancet* 1991; **338**: 252.
5. Bain PG, *et al.* Paraplegia after iopamidol myelography. *Lancet* 1991; **338**: 252–3.
6. Klein KM, *et al.* Status epilepticus and seizures induced by iopamidol myelography. *Seizure* 2004; **13**: 196–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iopamidol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, iopamidol is rapidly eliminated, with up to 50% of the dose recovered unchanged in the urine within 2 hours; the elimination half-life is about 2 hours. It is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hemoray; Iopamiron; Opacrile; ***Austral.***: Isovue†; ***Austria***: Gastromiro; Jopamiro; Scanlux; ***Braz.***: Iopamiron; ***Canad.***: Isovue; ***Chile***: Radiomiron; ***China***: Iopamiro (典比乐); ***Cz.***: Iopamigita; Scanlux; ***Fr.***: Iopamiron; ***Ger.***: Iopamigita; Iopathek; Solutrast; Unilux; ***Gr.***: Iopamiro; Radoso; Scanlux; ***Hong Kong***: Iopamiro†; ***Hung.***: Iopamiro; Scanlux; ***Irl.***: Gastromiro; Niopam; ***Israel***: Iopamiro; ***Ital.***: Gastromiro; Iopamiro; Iopasen; Scanlux; ***Mex.***: Pamiray†; ***Neth.***: Gastromiro; Iopamigita; Iopamiro; Scanlux†; ***NZ***: Iopamiro†; Isovue; ***Port.***: Gastromiro; Iopamiro; Scanlux; ***Rus.***: Iopamiro (Йопамиро); ***Singapore***: Iopamiro; ***Spain***: Iopamiro; Scanlux; ***Switz.***: Iopamiro; Scanlux; ***Turk.***: Iopamiro; Minotriyod; Pamiray; ***UK***: Gastromiro; Niopam; Scanlux; ***USA***: Isovue; ***Venez.***: Iopamiron.

Pharmacopoeial Preparations
BP 2014: Iopamidol Injection; Iopamidol Oral Solution;
USP 36: Iopamidol Injection.

Iopanoic Acid *(BAN, rINN)*

Acide Iopanoïque; Ácido iopanoico; Acidum Iopanoicum; Iodopanoic Acid; Iopanoico, ácido; Iopansäure; Jopaanihappo; Jopano rūgštis; Jopānsav; Jopansyra; Kyselina jopanoová; Иопаноевая Кислота.

2-(3-Amino-2,4,6-tri-iodobenzyl)butyric acid.

$C_{11}H_{12}I_3NO_2$=570.9

CAS — 96-83-3.

ATC — V08AC06.

ATC Vet — QV08AC06.

UNII — FE9794P71J.

Description. Iopanoic acid contains about 66.7% of I.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Iopanoic Acid). A white or yellowish-white powder. Practically insoluble in water; soluble in dehydrated alcohol and in methyl alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Iopanoic Acid). A cream-coloured powder, with a faint characteristic odour. Insoluble in water; soluble in alcohol, in chloroform, in ether, and in solutions of alkali hydroxides and carbonates. Store in airtight containers. Protect from light.

Profile

Iopanoic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It has been given orally for cholecystography and cholangiography in usual doses of 3 g, with plenty of water, about 10 to 14 hours before X-ray examination.

Iopanoic acid has also been used in the management of hyperthyroidism (see below).

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving iopanoic acid and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Hyperthyroidism. Iopanoic acid and other iodinated oral cholecystographic agents reduce conversion of thyroxine to tri-iodothyronine, as well as inhibiting release of thyroid hormones from the thyroid gland,[1] and they have been used in the management of hyperthyroidism (p. 2332.2). Iopanoic acid has been used successfully for pre-operative preparation in severe hyperthyroidism,[2-4] and for control of hyperthyroidism before radio-iodine treatment.[5] It has a rapid effect but rebound hyperthyroidism may occur and it is not generally suitable for long-term use.[1]

1. Braga M, Cooper DS. Oral cholecystographic agents and the thyroid. *J Clin Endocrinol Metab* 2001; **86**: 1853–60.
2. Pandey CK, *et al.* Rapid preparation of severe uncontrolled thyrotoxicosis due to Graves' disease with iopanoic acid—a case report. *Can J Anesth* 2004; **51**: 38–40.
3. Dhillon KS, *et al.* Treatment of hyperthyroidism associated with thyrotropin-secreting pituitary adenomas with iopanoic acid. *J Clin Endocrinol Metab* 2004; **89**: 708–11.
4. Panzer C, *et al.* Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab* 2004; **89**: 2142–4.
5. Bal CS, *et al.* Effect of iopanoic acid on radioiodine therapy of hyperthyroidism: long-term outcome of a randomized controlled trial. *J Clin Endocrinol Metab* 2005; **90**: 6536–40.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***India***: Iopac; ***Spain***: Colegraf†.

Pharmacopoeial Preparations
BP 2014: Iopanoic Acid Tablets;
USP 36: Iopanoic Acid Tablets.

Iopentol *(BAN, USAN, rINN)*

Compound 5411; Iopentolum; Jopentol; Jopentoli; Йопентол.

N,N'-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxy-3-methoxypropyl)acetamido]-2,4,6-tri-iodoisophthalamide.

$C_{20}H_{28}I_3N_3O_9$=835.2

CAS — 89797-00-2.

ATC — V08AB08.

ATC Vet — QV08AB08.

UNII — 7D6XWX076T.

Description. Iopentol contains about 45.6% of I.

Profile

Iopentol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, orally, or by instillation into body cavities, and is used in procedures including angiography, arthrography, endoscopic retrograde cholangiopancreatography, hysterosalpingography, urography, and visualisation of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Iopentol is usually available as solutions containing 32.9 to 76.8% of iopentol (equivalent to 150 to 350 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Imagopaque†; ***Fr.***: Ivepaque†; ***Gr.***: Imagopaque.

Iopodic Acid *(BANM, rINNM)*

Acide Iopodique; Ácido iopódico; Acidum Iopodicum; Iopódico, ácido; Ipodic Acid; Йодовая Кислота.

3-(3-Dimethylaminomethyleneamino-2,4,6-tri-iodophenyl) propionic acid.

$C_{12}H_{13}I_3N_2O_2$=598.0

CAS — 5587-89-3.

ATC — V08AC08; V08AC10.

ATC Vet — QV08AC08; QV08AC10.

UNII — F604ZKI910.

Calcium Iopodate *(BANM, rINNM)*

Calcii Iopodas; Calcium Ipodate; Iopodate Calcique; Iopodato cálcico; Ipodate Calcium; Kalciumjopodat; Kalsiumjopodaatti; Кальций Йоподат.

$(C_{12}H_{12}I_3N_2O_2)_2Ca$=1234.0

CAS — 1151-11-7.

ATC — V08AC10.

ATC Vet — QV08AC10.

UNII — 5057W5M9ZZ.

Description. Calcium Iopodate contains about 61.7% of I.

Sodium Iopodate *(BAN, rINN)*

Iopodate de Sodium; Iopodato de sodio; Ipodate Sodium (USAN); Natrii Iopodas; Natriumjopodaatti; Natriumjopodat; NSC-106962; Sodium Ipodate; Натрий Йоподат.

$C_{12}H_{12}I_3N_2NaO_2$=619.9

CAS — 1221-56-3.

ATC — V08AC08.

ATC Vet — QV08AC08.

UNII — F316LLW9WW.

Description. Sodium Iopodate contains about 61.4% of I.

Pharmacopoeias. In *US*.

USP 36: (Ipodate Sodium). A fine, white or off-white, odourless, crystalline powder. Soluble 1 in less than 1 of water, 1 in 2 of alcohol, 1 in 2 of dimethylacetamide, and 1 in 3.5 of dimethylformamide and of dimethyl sulfoxide; very slightly soluble in chloroform; freely soluble in methyl alcohol. Store in airtight containers.

Profile

Iopodic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1). It has similar properties to iopanoic acid (above) and has been used orally as the sodium or calcium salt for cholecystography and cholangiography. It has also been tried in the management of hyperthyroidism.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Gr.***: Biloptin.

Pharmacopoeial Preparations
USP 36: Ipodate Sodium Capsules.

Iopromide *(BAN, USAN, rINN)*

Iopromid; Iopromida; Iopromidum; Jopromid; Jopromidi; ZK-35760; Йопромид.

N,N'-Bis(2,3-dihydroxypropyl)-2,4,6-tri-iodo-5-(2-methoxyacetamido)-*N*-methylisophthalamide.

$C_{18}H_{24}I_3N_3O_8$=791.1

CAS — 73334-07-3.

ATC — V08AB05.

ATC Vet — QV08AB05.

UNII — 712BAC33MZ.

Description. Iopromide contains about 48.1% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Iopromide). Iopromide is a mixture of diastereoisomers and atropisomers. A white or slightly yellowish powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol and in acetone. Protect from light.

USP 36: (Iopromide). A white to slightly yellow powder. Freely soluble in water and in dimethyl sulfoxide; practically insoluble in alcohol, in acetone, and in ether. Protect from light.

Uses and Administration

Iopromide is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1). It may be given intravenously, intra-arterially, or by instillation into body cavities, and is used in procedures including angiography, arthrography, hysterosalpingography, urography, and assessment of dialysis shunt patency. It is also used for contrast enhancement during computed tomography.

Iopromide is usually available as solutions containing 31.2 to 76.9% of iopromide (equivalent to 150 to 370 mg/mL of iodine) and the dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1. Crystallisation and precipitation of iopromide has occurred from concentrated solutions; any preparation so affected should not be used.

References.
1. Kopp AF, *et al.* Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. *Acta Radiol* 2008; 49: 902–11.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies iopromide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, iopromide is rapidly distributed in the extracellular fluid. It is not metabolised and is eliminated unchanged in the urine; about 2% of a dose is excreted in faeces. An elimination half-life of about 2 hours has been reported; about 60% of a dose is excreted in urine within 3 hours and about 92% within 24 hours. Iopromide is not significantly bound to plasma proteins.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clarograf; ***Austral.***: Ultravist; ***Austria***: Ultravist; ***Belg.***: Ultravist; ***Canad.***: Ultravist; ***China***: Ultravist (优维显); ***Cz.***: Ultravist; ***Denm.***: Ultravist; ***Fin.***: Ultravist; ***Fr.***: Ultravist; ***Ger.***: Ultravist; ***Gr.***: Ultravist; ***Hung.***: Ultravist; ***Irl.***: Ultravist; ***Israel***: Ultravist; ***Ital.***: Ultravist; ***Jpn***: Proscope; ***Neth.***: Ultravist; ***Norw.***: Ultravist; ***NZ***: Ultravist; ***Port.***: Ultravist; ***Rus.***: Ultravist (Ультравист); ***S.Afr.***: Ultravist; ***Spain***: Clarograf†; Ultravist; ***Swed.***: Ultravist; ***Switz.***: Ultravist; ***Turk.***: Ultravist; ***UK***: Ultravist; ***USA***: Ultravist.

Pharmacopoeial Preparations
USP 36: Iopromide Injection.

Iopydol *(BAN, USAN, pINN)*

Iopidol; Iopydolum; Jopydol; Jopydoli; Йопидол.
1-(2,3-Dihydroxypropyl)-3,5-di-iodo-4-pyridone.
$C_8H_9I_2NO_3$=421.0
CAS — 5579-92-0.
ATC — V08AD02.
ATC Vet — QV08AD02.
UNII — T4661K682A.

Description. Iopydol contains about 60.3% of I.

Profile

Iopydol is an iodinated radiographic contrast medium (p. 1580.1) that has been used with iopydone for bronchography.

Iopydone *(BAN, USAN, rINN)*

Iopidona; Iopydonum; Йопидон.
3,5-Di-iodo-4-pyridone.
$C_5H_3I_2NO$=346.9
CAS — 5579-93-1.
UNII — J6B56XB19T.

Description. Iopydone contains about 73.2% of I.

Profile

Iopydone is an iodinated radiographic contrast medium (p. 1580.1) that has been used with iopydol for bronchography.

Iosarcol *(pINN)*

Iosarcolum; Йозаркол.
3,5-Diacetamido-2,4,6-triiodo-*N*-methyl-*N*-[[methyl(D-*gluco*-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]methyl]benzamide.
$C_{21}H_{29}I_3N_4O_9$=862.2
CAS — 97702-82-4.
UNII — 4D5D895OGC.

Description. Iosarcol contains about 44.2% of I.

Profile

Iosarcol is an iodinated nonionic monomeric contrast medium (p. 1580.1) used for a wide range of radiographic imaging procedures.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Melitrast†; ***Ger.***: Melitrast.

Iotalamic Acid *(BAN, rINN)*

Acide Iotalamique; Ácido Iotalámico; Acidum Iotalamicum; Iotalámico, ácido; Iotalaminsäure; Iothalamic Acid (USAN); Iothalamic Acid; Jotalaamihappo; Jotalaminsav; Jotalamo rūgštis; Jotalamsyra; Kyselina jotalamová; Methalamic Acid; MI-216; Йоталамовая Кислота.
5-Acetamido-2,4,6-tri-iodo-*N*-methylisophthalamic acid.
$C_{11}H_9I_3N_2O_4$=613.9
CAS — 2276-90-6.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — 16CHD79MIX.

Description. Iotalamic acid contains about 62% of I.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Iothalamic Acid). A white, odourless, powder. Slightly soluble in water and in alcohol; soluble in solutions of alkali hydroxides. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Iotalamate *(BANM, rINNM)*

Iotalamate de Méglumine; Iotalamato de meglumina; Iothalamate Meglumine; Meglumine Iothalamate; Meglumini Iotalamas; Меглумина Йоталамат.
The *N*-methylglucamine salt of iotalamic acid.
$C_{11}H_9I_3N_2O_4.C_7H_{17}NO_5$=809.1
CAS — 13087-53-1.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — XUW72GOP7W.

Description. Meglumine iotalamate contains about 47.1% of I.

Pharmacopoeias. *US* includes only as various injections.

Sodium Iotalamate *(BANM, rINNM)*

Iotalamate de Sodium; Iotalamato de sodico; Iotalamato de sodio; Iothalamate Sodium; Natrii Iotalamas; Sodium Iothalamate; Натрий Йоталамат.
$C_{11}H_8I_3N_2NaO_4$=635.9
CAS — 17692-74-9; 1225-20-3.
ATC — V08AA04.
ATC Vet — QV08AA04.
UNII — KDN276D83N.

Description. Sodium iotalamate contains about 59.9% of I.

Pharmacopoeias. *US* includes only as various injections.

Uses and Administration

Iotalamic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to the amidotrizoates (p. 1581.3). It may be given intravenously, intra-arterially, or by instillation into the bladder or uterus, and is used in procedures including angiography, arthrography, cholangiography, urography and hysterosalpingography. It is also used for contrast enhancement in computed tomography. Iotalamates have also been given orally or rectally for imaging of the gastrointestinal tract.

Iotalamic acid is usually available as solutions containing up to 54% of sodium iotalamate or up to 60% of meglumine iotalamate. The dose and strength used vary according to the procedure and route. A mixture of the two salts has been given to minimise adverse effects.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1.

Incidence of adverse effects. In 40 patients who underwent phlebography with 60% meglumine iotalamate minor adverse reactions were common despite the use of saline flushing and muscle contraction to clear the veins after examination.[1] The commonest effect was pain at the site of injection, or in the calf and foot; 15 patients of those who had pain in the calf or foot were found to have venous thrombosis. Major complications of phlebography appear to be rare but can cause serious morbidity; examination of 200 case notes and a retrospective study involving 3060 patients revealed 4 cases of necrosis in the skin of the foot and gangrene of the foot in 2.

1. Thomas ML, MacDonald LM. Complications of ascending phlebography of the leg. *BMJ* 1978; ii: 317–18.

Pharmacokinetics

On intravascular use the iotalamates are rapidly distributed; suitable concentrations for urography reach the urinary tract within 3 to 8 minutes of a bolus intravenous injection. Protein binding is reported to be low. The iotalamates are eliminated by the kidneys. In patients with normal renal function more than 90% of the dose injected is excreted in urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Small amounts are reported to be excreted via the bile in the faeces. The iotalamates are removed by peritoneal dialysis and haemodialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Conray; Cysto-Conray ***Austral.***: Conray; ***Canad.***: Conray; Cysto-Conray; Vascoray† ***Irl.***: Conray; ***UK***: Conray; ***USA***: Conray; Cysto-Conray.

Pharmacopoeial Preparations
USP 36: Iothalamate Meglumine and Iothalamate Sodium Injection; Iothalamate Meglumine Injection; Iothalamate Sodium Injection.

Iotrolan *(BAN, USAN, rINN)*

Iotrol; Iotrolán; Iotrolane; Iotrolanum; Iotrolum; Jotrolaani; Jotrolan; ZK-39482; Йотролан.
N,N′,N″,N‴-Tetrakis(2,3-dihydroxy-1-hydroxymethylpropyl)-2,2′,4,4′,6,6′-hexaiodo-5,5′-(*N,N′*-dimethylmalonyldi-imino) di-isophthalamide.
$C_{37}H_{48}I_6N_6O_{18}$=1626.2
CAS — 79770-24-4.
ATC — V08AB06.
ATC Vet — QV08AB06.
UNII — 16FL47B687.

Description. Iotrolan contains about 46.8% of I.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Iotrolan). A white or yellowish-white, hygroscopic powder. Very soluble in water; practically insoluble in alcohol; freely soluble in dimethyl sulfoxide. Store in airtight containers. Protect from light.

Uses and Administration

Iotrolan is a nonionic dimeric iodinated radiographic contrast medium (p. 1580.1). It is given intrathecally for myelography and for contrast enhancement in computed tomography, and by instillation into body ducts or cavities for procedures including lymphography, arthrography, hysterosalpingography, cholangiopancreatography, and for visualisation of the mammary ducts. It may also be given orally for imaging of the gastrointestinal tract.

Iotrolan is usually available as solutions containing 51.3% or 64.1% of iotrolan (equivalent to 240 or 300 mg/mL of iodine, respectively) and the dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

As for the amidotrizoates, p. 1582.1 and p. 1583.1. For the adverse effects relating to the use of nonionic contrast media such as iotrolan for myelography, see under Iohexol, p. 1590.2.

Pharmacokinetics

Iotrolan is excreted unchanged in the urine. After intrathecal injection, about 80% is excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Osmovist†; ***China***: Isovist (伊索显); ***Ger.***: Isovist; ***Gr.***: Isovist; ***Hung.***: Isovist†; ***Neth.***: Isovist†; ***NZ***: Isovist†; ***S.Afr.***: Isovist†; ***Switz.***: Isovist†; ***UK***: Isovist†.

Iotroxic Acid *(BAN, USAN, rINN)*

Acide Iotroxique; Ácido Iotróxico; Acidum Iotroxicum; Iotróxico, ácido; Jotroksihappo; Jotroxsyra; SH-213AB; Йотроксовая Кислота.
3,3′-(3,6,9-Trioxaundecanedioyldi-imino)bis(2,4,6-tri-iodobenzoic acid).
$C_{22}H_{18}I_6N_2O_9$=1215.8
CAS — 51022-74-3.

ATC — V08AC02.
ATC Vet — QV08AC02.
UNII — 84CSPTP9X6.

Description. Iotroxic acid contains about 62.6% of I.

Pharmacopoeias. In *Int.* and *Jpn.*

Meglumine Iotroxate *(BANM, rINNM)*

Dimeglumine Iotroxate; Iotroxate de Méglumine; Iotroxate Meglumine; Iotroxato de meglumina; Meglumine Iotroxinate; Meglumini Iotroxas; Меглумина Йотроксат.

The di(*N*-methylglucamine)salt of iotroxic acid.

$C_{22}H_{18}I_6N_2O_9.2C_7H_{17}NO_5$=1606.2

CAS — 68890-05-1.
ATC — V08AC02.
ATC Vet — QV08AC02.
UNII — 389136RRO0.

Description. Meglumine iotroxate contains about 47.4% of I.

Uses and Administration

Iotroxic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1); it is taken up by the liver and excreted in bile, and is used in cholecystography and cholangiography.

Iotroxic acid is given intravenously as a solution containing 10.5% of the meglumine salt. The usual dose is 10.5 g of meglumine iotroxate (equivalent to about 5 g of iodine), given by infusion over at least 30 minutes. Alternatively, a solution containing 22.8% of meglumine iotroxate may be used.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Pharmacokinetics

After intravenous injection, iotroxic acid binds to plasma proteins and is taken up by the liver; plasma-protein binding is about 60 to 90%. It is excreted primarily unchanged in the bile; a small amount is metabolised and excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Biliscopin; ***Austria***: Biliscopin; ***Ger.***: Biliscopin†; ***Gr.***: Biliscopin; ***NZ***: Biliscopin†; ***Switz.***: Biliscopin†; ***UK***: Biliscopin.

Ioversol *(BAN, USAN, rINN)*

Ioversolum; Joversol; Joversoli; MP-328; Йоверсол.

N,N'-Bis(2,3-dihydroxypropyl)-5-[*N*-(2-hydroxyethyl)glycolamido]-2,4,6-tri-iodoisophthalamide.

$C_{18}H_{24}I_3N_3O_9$=807.1

CAS — 87771-40-2.
ATC — V08AB07.
ATC Vet — QV08AB07.
UNII — N3RIB7X24K.

Description. Ioversol contains about 47.2% of I.

Pharmacopoeias. In *US.*

USP 36: (Ioversol). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Ioversol is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1) that is given intra-arterially or intravenously for angiography and urography. It is also used for contrast enhancement during computed tomography. It is usually available as a solution containing 34 to 74% of ioversol (equivalent to 160 to 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

References.
1. Floriani I, *et al.* Clinical profile of ioversol: a metaanalysis of 57 randomized, double-blind clinical trials. *Invest Radiol* 1996; 31: 479–91.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Hypersensitivity. A report[1] of a fatal anaphylactoid reaction to ioversol.

1. Jansman FGA, *et al.* Fatal anaphylactoid reaction following ioversol administration. *Pharm World Sci* 2007; 29: 584–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ioversol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

When given intravascularly, ioversol is rapidly eliminated unchanged in the urine, with a half-life of about 1.5 hours; more than 95% of a dose is eliminated within 24 hours. Binding to plasma or serum proteins is very low.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Optiray; ***Austral.***: Optiray; ***Austria***: Optiray; ***Belg.***: Optiject; Optiray; ***Canad.***: Optiray; ***Cz.***: Optiray; ***Denm.***: Optiray; ***Fin.***: Optiray; ***Fr.***: Optiject; Optiray; ***Gr.***: Optiray; ***Hung.***: Optiray; ***Irl.***: Optiray; ***Ital.***: Optiray; ***Neth.***: Optiray; ***Norw.***: Optiray; ***Port.***: Optiray; ***Rus.***: Optiray (Оптирей); ***Spain***: Optiray; ***Swed.***: Optiray; ***Switz.***: Optiray; ***UK***: Optiray; ***USA***: Optiray.

Pharmacopoeial Preparations
USP 36: Ioversol Injection.

Ioxaglic Acid *(BAN, USAN, rINN)*

Acide Ioxaglique; Ácido ioxáglico; Acidum Ioxaglicum; Ioxáglico, ácido; Ioxaglinsäure; Joksagliinihappo; Joksagliko rūgštis; Joxaglinsav; Joxaglinsyra; Kyselina joxaglová; P-286; Йоксагловая Кислота.

N-(2-Hydroxyethyl)-2,4,6-tri-iodo-5-[2',4',6'-tri-iodo-3'-(*N*-methylacetamido)-5'-methylcarbamoylhippuramido]isophthalamic acid.

$C_{24}H_{21}I_6N_5O_8$=1268.9

CAS — 59017-64-0.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — Z40X7EI2AF.

Description. Ioxaglic acid contains about 60% of I.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Ioxaglic Acid). A white or almost white hygroscopic powder. Very slightly soluble in water and in dichloromethane; slightly soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Ioxaglic Acid). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Meglumine Ioxaglate *(BANM, rINNM)*

Ioxaglate de Méglumine; Ioxaglate Meglumine (USAN); Ioxaglato de meglumina; Meglumini Ioxaglas; MP-302 (meglumine ioxaglate with sodium ioxaglate); Меглумина Йоксаглат.

The *N*-methylglucamine salt of ioxaglic acid.

$C_{24}H_{21}I_6N_5O_8.C_7H_{17}NO_5$=1464.1

CAS — 59018-13-2.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — 75JR975T11.

Description. Meglumine ioxaglate contains about 52% of I.

Sodium Ioxaglate *(BANM, rINNM)*

Ioxaglate de Sodium; Ioxaglate Sodium (USAN); Ioxaglato sódico; MP-302 (sodium ioxaglate with meglumine ioxaglate); Natrii Ioxaglas; Natriumjoksaglaatti; Natriumjoxaglat; Натрий Йоксагдат.

$C_{24}H_{20}I_6N_5NaO_8$=1290.9

CAS — 67992-58-9.
ATC — V08AB03.
ATC Vet — QV08AB03.
UNII — HQ43CN02U9.

Description. Sodium ioxaglate contains about 59% of I.

Uses and Administration

Ioxaglic acid is an ionic dimeric iodinated radiographic contrast medium (p. 1580.1). It is given intravenously, intra-arterially, intra-articularly, or by instillation into body ducts and cavities and is used in diagnostic procedures including angiography, arthrography, hysterosalpingography, and urography. It is also used for contrast enhancement during computed tomography.

Ioxaglic acid is usually available as solutions containing a mixture of the sodium and meglumine salts. Commonly used solutions contain 39.3% of meglumine ioxaglate and 19.6% of sodium ioxaglate (equivalent to 320 mg/mL of iodine) or 24.6% of meglumine ioxaglate and 12.3% of sodium ioxaglate (equivalent to 200 mg/mL of iodine). The dose and strength used depend upon the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ioxaglic acid as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Pharmacokinetics

On intravascular use, ioxaglates are rapidly distributed throughout the extracellular fluid. Protein binding is reported to be very low. They are mainly excreted unchanged in the urine, although biliary excretion may predominate in renal impairment. With normal renal function, about 90% of a dose is excreted in the urine within 24 hours; an elimination half-life of about 90 minutes has been reported. Ioxaglates cross the placenta and are distributed into breast milk. They are removed by haemodialysis and peritoneal dialysis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Hexabrix; ***Austral.***: Hexabrix; ***Austria***: Hexabrix; ***Belg.***: Hexabrix; ***Canad.***: Hexabrix; ***Chile***: Hexabrix; ***Cz.***: Hexabrix; ***Denm.***: Hexabrix†; ***Fin.***: Hexabrix; ***Fr.***: Hexabrix; ***Ger.***: Hexabrix; ***Gr.***: Hexabrix; ***Hung.***: Hexabrix; ***Irl.***: Hexabrix; ***Israel***: Hexabrix; ***Ital.***: Hexabrix; ***Neth.***: Hexabrix; ***Norw.***: Hexabrix; ***NZ***: Hexabrix; ***Port.***: Hexabrix; ***Spain***: Hexabrix; ***Swed.***: Hexabrix; ***Switz.***: Hexabrix; ***Turk.***: Hexabrix; ***UK***: Hexabrix; ***USA***: Hexabrix; ***Venez.***: Hexabrix.

Multi-ingredient Preparations. ***Thai.***: Hexabrix.

Pharmacopoeial Preparations
USP 36: Ioxaglate Meglumine and Ioxaglate Sodium Injection.

Ioxilan *(USAN, rINN)*

Ioxilan; Ioxilane; Ioxilanum; Ioxitol; Йоксилан.

N-(2,3-Dihydroxypropyl)-5-[*N*-(2,3-dihydroxypropyl)acetamido]-*N'*-(2-hydroxyethyl)-2,4,6-triidoisophthalamide.

$C_{18}H_{24}I_3N_3O_8$=791.1

CAS — 107793-72-6.
ATC — V08AB12.
ATC Vet — QV08AB12.
UNII — A4YJ7J11TG.

Description. Ioxilan contains about 48.1% of I.

Pharmacopoeias. In *US.*

USP 36: (Ioxilan). A white to off-white, practically odourless, powder. Soluble in water and in methyl alcohol. pH of a 10% solution in water is between 5.0 and 7.5. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Ioxilan is a nonionic monomeric iodinated radiographic contrast medium (see p. 1580.1). It is given intra-arterially or intravenously for procedures including angiography and urography; it is also used for contrast enhancement during computed tomography.

Ioxilan is usually available as solutions containing 62.3 or 72.7% of ioxilan (equivalent to 300 or 350 mg/mL of iodine). The dose and strength used vary according to the procedure and route.

Adverse Effects, Treatment, and Precautions

See under the amidotrizoates, p. 1582.1 and p. 1583.1.

Pharmacokinetics

After intravascular use, ioxilan is rapidly eliminated unchanged in the urine; about 94% of a dose is excreted within 24 hours. Protein binding is reported to be very low. Ioxilan is dialysable.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Imagenil; *Turk.*: Oxilan; *USA*: Oxilan.

Pharmacopoeial Preparations
USP 36: Ioxilan Injection.

Ioxitalamic Acid *(rINN)*

Acide Ioxitalamique; Ácido ioxitalámico; Acidum Ioxitalamicum; AG-58107; Ioxitalámico, ácido; Ioxithalamic Acid; Joksitalaamihappo; Joxitalamsyra; Йокситаламовая Кислота.

5-Acetamido-*N*-(2-hydroxyethyl)-2,4,6-tri-iodoisophthalamic acid.

$C_{12}H_{11}I_3N_2O_5$=643.9

CAS — 28179-44-4.
ATC — V08AA05.
ATC Vet — QV08AA05.
UNII — 967RDI7Z6K.

Description. Ioxitalamic acid contains about 59.1% of I.

Pharmacopoeias. In *Fr.*

Meglumine Ioxitalamate *(rINNM)*

Ioxitalamate de Méglumine; Ioxitalamate Meglumine; Ioxitalamato de meglumina; Meglumini Ioxitalamas; Меглумина Йокситаламат.

The *N*-methylglucamine salt of ioxitalamic acid.

$C_{12}H_{11}I_3N_2O_5.C_7H_{17}NO_5$=839.2

CAS — 29288-99-1.
ATC — V08AA05.
ATC Vet — QV08AA05.

Description. Meglumine ioxitalamate contains about 45.4% of I.

Sodium Ioxitalamate *(rINNM)*

Ioxitalamate de Sodium; Ioxitalamate Sodium; Ioxitalamato sódico; Natrii Ioxitalamas; Натрий Йокситаламат.

$C_{12}H_{10}I_3N_2NaO_5$=665.9

CAS — 33954-26-6.
ATC — V08AA05.
ATC Vet — QV08AA05.

Description. Sodium ioxitalamate contains about 57.2% of I.

Profile

Ioxitalamic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of the amidotrizoates (p. 1582.1). It is given intravenously or by instillation into body cavities for procedures including angiography, cholangiography, cystography, hysterosalpingography, and urography; it may be given orally or rectally for imaging of the gastrointestinal tract. It is also used for contrast enhancement in computed tomography.

Ioxitalamic acid is usually available as a solution containing 21% of the sodium salt (equivalent to 120 mg/mL of iodine), 55.1 to 66% of the meglumine salt (equivalent to 250 to 300 mg/mL of iodine), or as a mixture of both salts. The dose and strength used vary according to the procedure and route.

Monoethanolamine ioxitalamate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Telebrix 30; Telebrix 38; Telebrix Coronario; Telebrix Hystero; *Belg.*: Telebrix Gastro; Telebrix Hystero; Telebrix; *Canad.*: Telebrix; *Chile*: Telebrix 30; Telebrix 35; Cz.: Telebrix 30; Telebrix 35; Telebrix Gastro; *Fr.*: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; *Ger.*: Telebrix Gastro; Telebrix N 180 and 300; *Gr.*: Telebrix 30; Telebrix Gastro; Telebrix Hystero; Telebrix; *Hung.*: Telebrix Gastro†; Telebrix†; *Israel*: Telebrix Gastro; Telebrix; *Mex.*: Telebrix†; *Neth.*: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; *Port.*: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; *Switz.*: Telebrix 12; Telebrix 30; Telebrix 35; Telebrix Gastro; Telebrix Hystero; *Thai.*: Telebrix 35; *Turk.*: Telebrix; *Venez.*: Telebrix 30; Telebrix 35; Telebrix Hystero.

Mangafodipir Trisodium *(BANM, USAN, rINNM)*

Mangafodipir trisódico; Mangafodipir Trisodique; Mangafodipirum Trinatricum; MnDPDP (mangafodipir); S-095 (mangafodipir); Win-59010-2 (mangafodipir); Win-59010; Тринатрий Мангафодипир.

Trisodium trihydrogen (*OC*-6-13)-[[*N*,*N*′-ethylenebis(*N*-[[3-hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl]methyl]glycine) 5,5′-bis(phosphato)](8-)] manganate(6-); Trisodium trihydrogen (*OC*-6-13)-*N*,*N*′-ethane-1,2-diylbis[*N*-[2-methyl-3-oxido-κ*O*-5-(phosphonatooxymethyl)-4-pyridylmethyl]glycinato(*O*,*N*)]manganate(II).

$C_{22}H_{27}MnN_4Na_3O_{14}P_2$=757.3

CAS — 155319-91-8 (mangafodipir); 140678-14-4 (mangafodipir trisodium).
ATC — V08CA05.
ATC Vet — QV08CA05.
UNII — 129FW80TG4.

Pharmacopoeias. In *US*.

USP 36: (Mangafodipir Trisodium). Pale yellow crystals or crystalline powder. Freely soluble in water; very slightly soluble in alcohol and in acetone; slightly soluble in chloroform; sparingly soluble in methyl alcohol. pH of a 1% solution in water is between 5.5 and 7.0. Store at a temperature not exceeding 8 degrees.

Uses and Administration

Mangafodipir is a manganese chelate that is used as a magnetic resonance contrast medium (p. 1580.1) for imaging of the liver and pancreas. Manganese has paramagnetic properties that increase the relaxivity of hydrogen ions, leading to signal enhancement. Free manganese is released from mangafodipir in the body and is taken up by normal liver and pancreatic tissue, increasing the degree of contrast.

Mangafodipir is given intravenously as the trisodium salt.

In the UK, a solution containing mangafodipir trisodium 7.57 mg/mL (10 micromol/mL) is used. Usual doses for imaging are:

- liver: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 2 to 3 mL/minute
- pancreas: 0.5 mL/kg (5 micromol/kg) given by intravenous infusion at a rate of 4 to 6 mL/minute

In the USA, a more concentrated preparation is used, containing mangafodipir trisodium 37.9 mg/mL (50 micromol/mL). Usual doses are:

- liver: 0.1 mL/kg (5 micromol/kg), given by slow intravenous injection to a maximum dose of 15 mL

Adverse Effects and Precautions

The most common adverse effects of mangafodipir are injection site discomfort, feelings of warmth or flushing, headache, nausea, vomiting, abdominal pain, and taste disturbances. Hypersensitivity reactions, including anaphylactoid reactions, may occur. Transient increases in bilirubin and liver transaminase concentrations and decreases in plasma-zinc concentrations have been reported.

Mangafodipir should be used with caution in patients with hepatic or renal impairment and should be avoided if impairment is severe. It should not be given to patients with phaeochromocytoma.

References.

1. Federle MP, *et al.* Safety and efficacy of mangafodipir trisodium (MnDPDP) injection for hepatic MRI in adults: results of the U.S. multicenter phase III clinical trials (safety). *J Magn Reson Imaging* 2000; 12: 186–97.

Pharmacokinetics

After intravenous injection, mangafodipir is dephosphorylated and manganese is exchanged for zinc leading to the release of free manganese ions and the formation of 2 inactive metabolites. Manganese is rapidly taken up by the liver, pancreas, kidney and spleen; about 15 to 20% is excreted in the urine within 24 hours, with most of the remainder excreted in the faeces over about 4 days. The metabolites are almost entirely excreted in the urine within 24 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Teslascan†; *Belg.*: Teslascan†; *Canad.*: Teslascan; *Cz.*: Teslascan†; *Fr.*: Teslascan†; *Ger.*: Teslascan†; *Gr.*: Teslascan†; *Hung.*: Teslascan†; *Irl.*: Teslascan†; *Ital.*: Teslascan†; *Neth.*: Teslascan†; *Norw.*: Teslascan†; *NZ*: Teslascan; *Pol.*: Teslascan†; *Port.*: Teslascan†; *Rus.*: Teslascan (Тесласкан); *Spain*: Teslascan†; *Swed.*: Teslascan†; *Switz.*: Teslascan†; *Turk.*: Teslascan; *UK*: Teslascan†; *USA*: Teslascan†.

Pharmacopoeial Preparations
USP 36: Mangafodipir Trisodium Injection.

Metrizamide *(BAN, USAN, rINN)*

Metritsamidi; Metrizamid; Metrizamida; Métrizamide; Metrizamidum; Win-39103; Метризамид.

2-[3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzamido]-2-deoxy-D-glucose.

$C_{18}H_{22}I_3N_3O_8$=789.1

CAS — 31112-62-6 (metrizamide); 55134-11-7 (metrizamide, glucopyranose form).
ATC — V08AB01.
ATC Vet — QV08AB01.
UNII — RHH3W8F1CO.

Description. Metrizamide contains about 48.2% of I.

Profile

Metrizamide is a nonionic monomeric iodinated radiographic contrast medium (p. 1580.1) that has been used in myelography, angiography, intravenous urography, and arthrography, and also for contrast enhancement during computed tomography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizamide and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Metrizoic Acid *(BANM, rINNM)*

Acide Métrizoïque; Ácido metrizoico; Acidum Metrizoicum; Metritsoiinihappo; Metrizoico, ácido; Metrizoinsyra; Метризоевая Кислота.

3-Acetamido-2,4,6-tri-iodo-5-(*N*-methylacetamido)benzoic acid.

$C_{12}H_{11}I_3N_2O_4$=627.9

CAS — 1949-45-7.
ATC — V08AA02.
ATC Vet — QV08AA02.
UNII — CM1N99QR1M.

Description. Metrizoic acid contains about 60.6% of I.

Meglumine Metrizoate *(BANM, rINNM)*

Meglumini Metrizoas; Métrizoate de Méglumine; Metrizoate Meglumine; Metrizoato de meglumina; Меглумина Метризоат.

The *N*-methylglucamine salt of metrizoic acid.

$C_{12}H_{11}I_3N_2O_4.C_7H_{17}NO_5$=823.2

CAS — 7241-11-4.
ATC — V08AA02.
ATC Vet — QV08AA02.
UNII — RJY6JR42WQ.

Description. Meglumine metrizoate contains about 46.3% of I.

Sodium Metrizoate *(BAN, rINN)*

Métrizoate de Sodium; Metrizoate Sodium (USAN); Metrizoato de sodio; Natrii Metrizoas; NSC-107431; Натрия Метризоат.

$C_{12}H_{10}I_3N_2NaO_4$=649.9

CAS — 7225-61-8.
ATC — V08AA02.
ATC Vet — QV08AA02.
UNII — O65Q227UIC.

Description. Sodium metrizoate contains about 58.6% of I.

Profile

Metrizoic acid is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of the amidotrizoates (p. 1582.1). It has been used as the meglumine and sodium salts, often with calcium metrizoate and magnesium metrizoate, for a variety of diagnostic procedures including angiography, cholangiography, and hysterosalpingography.

Breast feeding. No adverse effects have been seen in breast-feeding infants whose mothers were receiving metrizoate and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/03/06)

Corticosteroids

The adrenal cortex synthesises both corticosteroids, based on a 21-carbon nucleus, and some sex hormones, mainly androgens, based on a 19-carbon nucleus. The corticosteroids are traditionally divided into those with mainly glucocorticoid actions, of which cortisol (hydrocortisone) is the most important endogenous example, and those that are mainly mineralocorticoid, of which aldosterone is much the most important.

The endogenous glucocorticoids are under regulatory control from the hypothalamus and pituitary, via the releasing hormones corticorelin (p. 1628.1) and corticotropin or ACTH (p. 1628.3). In return the glucocorticoids act to inhibit production and release of these releasing hormones by a negative feedback mechanism. The system is known collectively as the hypothalamic-pituitary-adrenal (HPA) axis. Aldosterone secretion, by contrast, is under the control of the renin-angiotensin system.

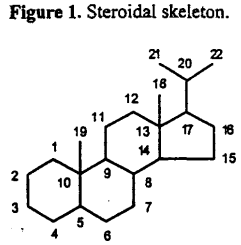
The main **mineralocorticoid** actions are on fluid and electrolyte balance. They enhance sodium reabsorption in the kidney and hence expand the extracellular fluid volume, and they enhance renal excretion of potassium and H^+.

The **glucocorticoid** actions are wide-ranging. They have potent anti-inflammatory and immunosuppressive effects, at least partly through inhibition of the release of various cytokines, and it is mainly these that are made use of clinically (see below). They also have profound metabolic effects: blood glucose concentrations are maintained or increased by a decrease in peripheral glucose utilization and an increase in gluconeogenesis; glycogen deposition, protein breakdown, and lipolysis are increased, and effects on calcium uptake and excretion lead to a decrease in body calcium stores. Glucocorticoids facilitate the action of many other active endogenous substances, and affect the function of cardiovascular system, kidneys, skeletal muscle and CNS.

Many synthetic congeners and derivatives of the corticosteroids are available. The main corticosteroids used systemically are hydroxy compounds (alcohols). They are relatively insoluble in water and the sodium salt of the phosphate or succinate ester is generally used to provide water-soluble forms for injections or solutions. Such esters are readily hydrolysed in the body.

Various structure-activity relationships are understood for the corticosteroids and have been made use of in the development of new compounds. The presence of a hydroxyl group at position 11 seems to be essential for glucocorticoid activity, while a hydroxyl at position 21 is required for mineralocorticoid activity. Fluorination at position 9 enhances both mineralocorticoid and glucocorticoid activity. Substitution at carbon 16 (as in betamethasone, dexamethasone, or triamcinolone) virtually eliminates mineralocorticoid activity. Esterification of corticosteroids at the 17 or 21 positions with fatty acids generally increases the topical activity. The formation of cyclic acetonides at the 16 and 17 positions further increases topical anti-inflammatory activity, usually without increasing systemic glucocorticoid activity. Figure 1 (below) shows the basic steroidal skeleton structure.

Figure 1. Steroidal skeleton.



In the medical and pharmacological literature the names of unesterified corticosteroids have frequently been used indiscriminately for both the unesterified and esterified forms and it is not always apparent to which form reference is being made. The unesterified form is sometimes qualified by the phrase 'free alcohol'.

Uses and Administration of Corticosteroids

The corticosteroids are used in physiological doses for replacement therapy in adrenal insufficiency. Pharmacological doses are used when palliative anti-inflammatory or immunosuppressant effects are required. Before instituting therapy the benefits and risks of corticosteroids should be considered; where appropriate, local rather than systemic therapy should be used. The lowest effective dose should be used for the shortest possible time; high doses may be needed for life-threatening situations.

The effects of different corticosteroids vary qualitatively as well as quantitatively, and it may not be possible to substitute one for another in equal therapeutic amounts without provoking adverse effects. Thus, whereas cortisone and hydrocortisone have very appreciable mineralocorticoid (or sodium-retaining) properties relative to their glucocorticoid (or anti-inflammatory) properties, prednisolone and prednisone have considerably less, and others, such as betamethasone and dexamethasone, have none or virtually none. In contrast, the mineralocorticoid properties of fludrocortisone are so pronounced that its glucocorticoid effects are considered to have no clinical significance.

As a rough guide, the approximate **equivalent doses** of the main corticosteroids in terms of their glucocorticoid (or anti-inflammatory) properties alone, are:

- betamethasone 750 micrograms
- cortisone acetate 25 mg
- dexamethasone 750 micrograms
- hydrocortisone 20 mg
- methylprednisolone 4 mg
- prednisolone 5 mg
- prednisone 5 mg
- triamcinolone 4 mg

However, esterification generally alters potency and compounds given at equivalent glucocorticoid doses may not have equivalent clinical effect.

The mineralocorticoid properties of corticosteroids (see above) are rarely used. Exceptions include the treatment of

primary adrenocortical insufficiency, in which both mineralocorticoid and glucocorticoid replacement is necessary, usually in the form of fludrocortisone with hydrocortisone (for details, see p. 1600.2). The mineralocorticoid properties of fludrocortisone are also used to maintain blood pressure in patients with orthostatic hypotension (see p. 1634.3).

The anti-inflammatory and immunosuppressant glucocorticoid properties of corticosteroids (see p. 1597.1) are used to suppress the clinical manifestations of disease in many disorders considered to have inflammatory or immunological components. For these purposes, the synthetic analogues with their considerably reduced mineralocorticoid properties linked with enhanced glucocorticoid properties, are preferred. Despite the existence of very powerful synthetic glucocorticoids with virtually no mineralocorticoid activity, the hazards of inappropriately high glucocorticoid therapy are such that the less powerful prednisolone and prednisone are the glucocorticoids of choice for most conditions, since they allow for a greater margin of safety. There is little to choose between prednisolone and prednisone; prednisolone is usually recommended in the UK since it exists in a metabolically active form, whereas prednisone is inactive and must be converted into its active form by the liver; hence, particularly in some liver disorders, bioavailability of prednisone is less reliable (but see Hepatic Impairment under Precautions of Prednisolone, p. 1646.3).

Because the therapeutic effects of corticosteroids seem to be of longer duration than the metabolic effects, intermittent treatment with corticosteroids has been used to allow the metabolic rhythm of the body to become re-established while maintaining the therapeutic effects. Regimens of intermittent therapy have usually consisted of short courses of treatment or of the use of single doses on alternate days. Such alternate-day therapy, however, is only appropriate for corticosteroids with a relatively short duration of action and small mineralocorticoid effect, such as prednisolone, and only in certain disease states. Corticosteroids are also given in single daily doses at times coinciding with maximum or minimum output of the adrenal cortex in order to obtain the desired effect on the adrenals (see Diurnal Effect under Administration, below).

Doses of corticosteroids higher than those required for physiological replacement will eventually lead to some degree of adrenal suppression, the extent depending on the dose given, and the route, frequency, time, and duration of treatment. The adrenal glands are considered to have a daily output equivalent to about 10 or 20 mg of hydrocortisone (cortisol), but individual blood-cortisol concentrations may vary widely, and can increase up to tenfold or more during stress. Therefore, during periods of stress or trauma, such as during and after surgery and when suffering from infections, the corticosteroid dosage of patients must be increased. In patients on long-term corticosteroid therapy undergoing surgery this is usually provided by parenteral hydrocortisone; graduated regimens tailored to the severity of surgery (see p. 1640.3) are now preferred to the former high-dose standard regimens tapered over 5 days, whose use has been questioned (see Surgery, under Administration, p. 1599.1).

Although the empirical use of a corticosteroid is appropriate in a life-threatening situation, generally it is advisable not to begin corticosteroid therapy until a definite diagnosis has been made, for otherwise symptoms may be masked to such an extent that a true diagnosis becomes extremely difficult to make and the disease may reach an advanced stage before detection.

Systemic therapy is indicated in many conditions. Where possible the oral route is preferred but parenteral doses may be used if the disease is severe or an emergency arises. Intravenous therapy is generally used for intensive emergency treatment as the onset of action is relatively fast although intramuscular injections, often formulated as longer-acting depot preparations, may also be used to provide subsequent cover. Examples of conditions treated with systemic corticosteroids include:

- as an adjunct to adrenaline in life-threatening allergic reactions such as angioedema or anaphylaxis (see p. 1293.2)
- some blood disorders, including auto-immune haemolytic anaemia (p. 1122.2) and immune thrombocytopenia (p. 1606.1)
- selected connective tissue and muscle disorders, such as Behçet's syndrome (p. 1601.1), polymyalgia rheumatica (p. 1610.3), polymyositis (p. 1611.1), SLE (p. 1613.3), and the vasculitic syndromes (p. 1615.2)
- some inflammatory eye disorders, particularly those affecting the posterior chamber such as uveitis (p. 1615.1)
- inflammatory gastrointestinal disorders, such as Crohn's disease and ulcerative colitis, although local administration by the rectal route may be preferred in some circumstances (see p. 1808.3)
- infections accompanied by a severe inflammatory component provided that appropriate anti-infective drugs are also given and that the benefits of corticosteroid therapy outweigh the possible risk of disseminated infection; examples of conditions where corticosteroid may be considered include helminthic infections, the Jarisch-Herxheimer reaction, and tuberculous meningitis (p. 1614.3)
- selected kidney disorders including lupus nephritis (see Systemic Lupus Erythematosus, p. 1613.3) and various glomerular disorders (p. 1604.3)
- selected liver disorders, including auto-immune chronic active hepatitis (p. 1602.3)
- some neurological disorders such as infantile spasms (see Epilepsy, p. 1604.1) and subacute demyelinating polyneuropathy (p. 1611.2); also in cerebral oedema (p. 1602.3), including that associated with malignancy
- some respiratory disorders, such as asthma (p. 1600.3, although inhaled corticosteroids are preferred to oral therapy for prophylaxis), interstitial lung disease (p. 1607.1), pulmonary sarcoid (p. 1612.2), and neonatal respiratory distress syndrome (p. 1608.3)
- some cases of rheumatoid arthritis, where recent evidence suggests there may be value in early treatment of active disease (see p. 1612.1)
- severe skin disorders such as pemphigus and pemphigoid (p. 1687.1)

Glucocorticoids are also used with antineoplastics in regimens for the management of malignant disease. They are also given to reduce immune responses after organ transplantations, often with other immunosuppressants (see p. 1932.2).

Corticosteroids are not now considered useful in patients with aspiration syndromes or stroke.

Intra-articular injection, in the absence of infection and with full aseptic precautions, may be used, for example, in the treatment of rheumatoid arthritis (p. 13.2), osteoarthritis (p. 12.3), and ankylosing spondylitis (see Spondyloarthropathies, p. 14.3). Either hydrocortisone acetate or one of the esters of the synthetic corticosteroids is used. It should be noted that there have been several reports of joint damage after the intra-articular injection of corticosteroids into load-bearing joints.

Topical application often produces dramatic suppression of skin diseases in which inflammation is a prominent feature, such as eczema (p. 1684.1), seborrhoeic dermatitis (p. 1689.1), and some forms of psoriasis (p. 1688.1). However, the disease may return or be exacerbated when corticosteroids are withdrawn and this appears to be a particular problem in some of the forms of psoriasis. Occasionally, corticosteroids may be used with the addition of a suitable antimicrobial, such as neomycin, in the treatment of infected skin. For comments on the topical application of preparations containing a corticosteroid and neomycin, see Adverse Effects of Neomycin, p. 330.2.

Intralesional injection sometimes hastens the resolution of chronic skin lesions such as lichen planus (p. 1685.2), alopecia areata (p. 1682.3), and keloids.

Topical application to the eye in inflammatory and traumatic disorders has led to dramatic results, but the occurrence of herpetic and fungal infections of the cornea and other serious complications are considerable obstacles, and eye drops containing corticosteroids should be used under strict ophthalmic supervision with regular checks of intra-ocular pressure. Care is also required when corticosteroids are given by **subconjunctival injection** in inflammatory eye disorders.

Ear drops containing corticosteroids are used in the treatment of otitis externa (see p. 195.1).

Inhalational therapy is widely used in the prophylaxis of asthma (p. 1600.3).

Nasal application is used in the prophylaxis and treatment of allergic and non-allergic rhinitis (see p. 612.1) and nasal polyps (p. 1608.2).

Rectal administration, by either suppository or enema, may be used for some corticosteroids, notably in the treatment of inflammatory bowel disease (p. 1808.3).

Administration

Diurnal effect. The diurnal rhythm of the adrenal cortex leads to about 70% of the daily secretion being made between midnight and 9 am.[1] In the treatment of adrenal cortical hyperplasia a dose of hydrocortisone given at night will be nearly twice as suppressive as the same dose given during the day. However, in treating allergic or collagen disease when suppression of adrenal cortical activity is best avoided a dose of hydrocortisone at about 8 am is indicated. When reducing corticosteroid dosage after treatment, a single dose given at 8 am will be most beneficial and will not inhibit corticotropin secretion. Also, for similar reasons,[2] when used for replacement therapy corticosteroids are given in unequal doses during the day (two-thirds of the daily dose in the morning, and one-third at night).

1. Demos CH, *et al.* A modified (once a day) corticosteroid dosage regimen. *Clin Pharmacol Ther* 1964; 5: 721–7.
2. Aronson JK. Chronopharmacology: reflections on time and a new text. *Lancet* 1990; 335: 1515–16.

Epidural route. Although epidural injections of corticosteroids have been widely used in the treatment of sciatica and chronic low back pain (p. 9.2), evidence of efficacy is lacking or conflicting, and guidelines do not recommend them for routine use.[1,2] Others have also reviewed epidural corticosteroid use.[3-6]

It should be noted that inadvertent intrathecal injection of corticosteroids has resulted in severe neurological complications.

1. Armon C, *et al.* Assessment: use of epidural steroid injections to treat radicular lumbosacral pain: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2007; 68: 723–9. Also available at: http://www.neurology.org/cgi/reprint/68/10/723.pdf (accessed 24/03/10)
2. Airaksinen O, *et al.* COST B13 Working Group on Guidelines for Chronic Low Back Pain. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. *Eur Spine J* 2006; 15 (suppl 2): S192–S300. Also available at: http://www.backpaineurope.org/web/files/WG2_Guidelines.pdf (accessed 24/03/10)
3. Abdi S, *et al.* Epidural steroids in the management of chronic spinal pain: a systematic review. *Pain Physician* 2007; 10: 185–212.
4. Young IA, *et al.* The use of lumbar epidural/transforaminal steroids for managing spinal disease. *J Am Acad Orthop Surg* 2007; 15: 228–38.
5. Stafford MA, *et al.* Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. *Br J Anaesth* 2007; 99: 461–73.
6. Valat JP, Rozenberg S. Local corticosteroid injections for low back pain and sciatica. *Joint Bone Spine* 2008; 75: 403–7.

Inhalational therapy. Corticosteroids are given by inhalation, particularly in the maintenance therapy of asthma, in order to deliver the drug directly to the lungs, at smaller doses than are needed orally, and minimise systemic adverse effects. Different inhaled corticosteroids differ in their potency, though there is little evidence of a difference in efficacy at recommended doses.[1] Of those widely available by inhalation, beclometasone dipropionate and budesonide have been considered to have similar potency, while flunisolide is less potent, and ciclesonide, fluticasone propionate, and mometasone furoate are considered to be more potent. However, formulation may affect drug availability; the replacement of chlorofluorocarbon propellants with a hydrofluoroalkane has increased the drug availability from some products, necessitating the use of lower doses[2,3] (see also Reformulation, under Beclometasone Dipropionate, p. 1622.3).

Efficient delivery to the bronchial tree is crucial and several different devices are available, including pressurised aerosol inhalers, breath-actuated aerosol inhalers, and dry powder inhalers. These devices appear to be equally effective for the delivery of corticosteroids.[4] However, many patients, especially children, find that inhalation is made much easier by fitting a spacer device to the inhaler.[5] Such a device is recommended when high doses are to be inhaled, to prevent oropharyngeal deposition and subsequent systemic absorption. However, the type of spacer used and the method of use may dramatically alter the amount of drug available for inhalation. The drug should be introduced into the spacer by single actuations, each followed by inhalation, with the delay between actuation of the inhaler and inhalation from the spacer kept to a minimum. In some spacers static electricity accumulates, and the build up of charge reduces drug delivery: this can be controlled by washing and drying the spacer in air once a month. Considerable differences in the dose delivered to the airways may also be seen between different types of nebuliser, and between nebulisers and spacer devices.[6]

It should be borne in mind that apparent differences in the dose supplied from inhaler devices in different countries may in some cases be artefacts, due to variations in the way the dose is measured or expressed. In the UK, for example, the dose supplied from a metered-dose inhaler is generally quoted as the amount released into the mouthpiece from the valve. In the USA, however, doses may be stated in terms of the amount of drug emitted from the mouthpiece, which due to drug deposition will be slightly less than the amount released from the valve.

1. Kelly HW. Comparison of inhaled corticosteroids: an update. *Ann Pharmacother* 2009; 43: 519–27.
2. Newman SP. Deposition and effects of inhaled corticosteroids. *Clin Pharmacokinet* 2003; 42: 529–44.
3. MHRA/CHM. Inhaled products that contain corticosteroids. *Drug Safety Update* 2008; 1 (12): 6–7. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON020567&RevisionSelectionMethod=LatestReleased (accessed 12/08/08)
4. Brocklebank D, *et al.* Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering corticosteroids in asthma. *BMJ* 2001; 323: 896–900.
5. O'Callaghan C, Barry PW. How to choose delivery devices for asthma. *Arch Dis Child* 2000; 82: 185–7.
6. O'Callaghan C, Barry P. Delivering inhaled corticosteroids to patients. *BMJ* 1999; 318: 410–11.

Intra-articular route. Intra-articular and periarticular injection of corticosteroids is an established treatment for a variety of joint and soft-tissue lesions.[1-4] Pain and

Perflenapent (USAN, rINN) ⊗

Dodecafluoropentanum; Dodekafluoropentaani; Dodekafluoropentan; Perflénapent; Perflenapentum; Перфленапент.

Dodecafluoropentane.

C_5F_{12}=288.0

CAS — 678-26-2.

ATC — V08DA03.

ATC Vet — QV08DA03.

UNII — 483AU1Y5CZ.

Profile

Perflenapent is a liquid perfluorocarbon that has been used as an ultrasound contrast medium (p. 1580.2) for echocardiography. It has been given intravenously as an emulsion containing droplets of perflenapent; on warming to body temperature the droplets form microbubbles of perflenapent gas that provide echo-enhancement. A small amount of perflisopent (below) was also included in the formulation.

References.

1. Robbin ML, Eisenfeld AJ. Perflenapent emulsion: a US contrast agent for diagnostic radiology—multicenter, double-blind comparison with a placebo. *Radiology* 1998; 207: 717–22.
2. Klemman DW, Wesley DJ. Safety assessment of perflenapent emulsion for echocardiographic contrast enhancement in patients with congestive heart failure or chronic obstructive pulmonary disease. *Am Heart J* 2000; 139: 1077–80.

Perflexane (USAN, rINN) ⊗

Perflexano; Perflexanum; Перфлексан.

Tetradecafluorohexane.

C_6F_{14}=338.0

CAS — 355-42-0.

UNII — FX3WJ41CMX.

Profile

Perflexane is a perfluorocarbon gas that has been used as an ultrasound contrast medium (p. 1580.2) for echocardiography. Dry microspheres containing the gas are reconstituted immediately before use, leading to the formation of microbubbles of perflexane that provide echo-enhancement; lipids are included in the microspheres to stabilise the bubbles when they form.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Imagent.

Perflisopent (USAN, rINN) ⊗

Perflisopentum; Перфлизопент.

Nonafluoro-2-(trifluoromethyl)butane.

C_5F_{12}=288.0

CAS — 594-91-2.

UNII — 40FAQ8ON24.

Profile

Perflisopent is a perfluorocarbon that has been used as an ultrasound contrast medium (p. 1580.2) with perflenapent (above) for echocardiography.

Perflubutane (USAN, rINN)

AI-700; Perflubutano; Perflubutanum; Perfluorobutane; Перфлубутан.

Decafluorobutane.

C_4F_{10}=238.0

CAS — 355-25-9.

UNII — SE4TWR0K2C.

NOTE. The name Imagify has been used as a trade mark for perflubutane.

Profile

Perflubutane is a perfluorocarbon ultrasound contrast medium (p. 1580.2) that is used as microspheres in the detection of focal liver lesions. It is under investigation in the assessment of myocardial perfusion.

References.

1. Senior R. Imagify® (perflubutane polymer microspheres) injectable suspension for the assessment of coronary artery disease. *Expert Rev Cardiovasc Ther* 2007; 5: 413–21.
2. Moriyasu F, Itoh K. Efficacy of perflubutane microbubble-enhanced ultrasound in the characterization and detection of focal liver lesions: phase 3 multicenter clinical trial. *Am J Roentg* 2009; 193: 86–95.
3. Takahashi M, *et al.* Contrast-enhanced ultrasound with perflubutane microbubble agent: evaluation of differentiation of hepatocellular carcinoma. *Am J Roentg* 2011; 196: W123–W131.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn:* Sonazoid.

Perflutren (BAN, USAN, rINN) ⊗

DMP-115; FS-069; MRX-115; Octafluoropropanum; Oktafluoropropaani; Oktafluoropropan; Perfluoropropane; Perflutrène; Perflutreno; Perflutrenum; Перфлутрен.

Octafluoropropane.

C_3F_8=188.0

CAS — 76-19-7.

UNII — CK0N3WH0SR.

Profile

Perflutren is a perfluorocarbon gas used as either albumin- or lipid-coated microspheres as an ultrasound contrast medium (p. 1580.2) for echocardiography.

- The *albumin-coated microspheres* are suspended in 1% albumin solution immediately before use and are given in a dose of 0.5 to 3 mL by intravenous injection, repeated if necessary up to a total dose of 8.7 mL.
- The *lipid-coated microsphere* suspension is formed by agitating the gas with a lipid solution immediately before use and is given in a dose of 10 microlitre/kg by intravenous injection, repeated once after 30 minutes if required, or as intravenous injections of 100 to 400 microlitres repeated as required up to a maximum total dose of 1.6 mL. Alternatively, 1.3 mL of the suspension may be diluted in 50 mL of sodium chloride 0.9% or glucose 5% and given by intravenous infusion at an initial rate of 4 mL/minute, adjusted as required, to a maximum rate of 10 mL/minute.

Serious cardiopulmonary reactions, including fatalities, have been reported with perflutren and it should be used with extreme caution and appropriate monitoring in patients with pulmonary hypertension or unstable cardiopulmonary conditions. The safety of perflutren has not been established in patients with right-to-left cardiac shunts; as it can enter the arterial circulation directly via such shunts, it should also be used with extreme caution or avoided in such patients.

Perflutren has been given by intra-ocular injection to provide tamponade in the management of retinal detachment.

Adverse effects. After reports of serious cardiopulmonary events, including several deaths, during or within 30 minutes of use of a microbubble contrast agent, in October 2007 the FDA required warnings and contra-indications to be added to the US licensed product information for perflutren. Contra-indications included worsening or unstable heart failure, acute myocardial infarction or coronary syndromes, serious ventricular arrhythmias, and conditions predisposing to pulmonary hypertension. Although 5 further fatalities associated with perflutren use had been reported as of July 2008, along with a further 60 reports of serious non-fatal adverse events, the FDA considered it appropriate to remove most of these contra-indications in the light of subsequent evidence.[1] The contrast medium continued to be contra-indicated in patients with right-to-left or bidirectional shunts, and intensive monitoring was considered indicated in patients with pulmonary hypertension or unstable cardiopulmonary conditions for 30 minutes after use. UK licensed product information notes the absence of safety data in patients with right-to-left shunts, and in those on mechanical ventilation, and advises caution in such patients.

Retrospective analyses of data from patients undergoing echocardiography[2-4] found no evidence that the incidence of adverse effects or death was increased in patients given perflutren.

1. FDA. Information for healthcare professionals: micro-bubble contrast agents (marketed as Definity (perflutren lipid microsphere) injectable suspension and Optison (perflutren protein-type A microspheres for injection)) (issued 17th July, 2008). Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm092270.htm (accessed 24/08/10)
2. Herzog CA. Incidence of adverse events associated with use of perflutren contrast agents for echocardiography. *JAMA* 2008; 299: 2023–5.
3. Kusnetzky LL, *et al.* Acute mortality in hospitalized patients undergoing echocardiography with and without an ultrasound contrast agent: results in 18,671 consecutive studies. *J Am Coll Cardiol* 2008; 51: 1704–6.
4. Dolan MS, *et al.* Safety and efficacy of commercially available ultrasound contrast agents for rest and stress echocardiography: a multicenter experience. *J Am Coll Cardiol* 2009; 53: 32–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria:* Optison; *Canad.:* Definity; *Chile:* Definity; *Cz.:* Luminity†; Optison; *Denm.:* Optison; *Fr.:* Luminity†; *Ger.:* Optison; *Gr.:* Optison; *Hung.:* Optison; *Irl.:* Luminity†; Optison; *Israel:* Definity; *Ital.:* Luminity†; Optison; *Neth.:* Luminity†; Optison; *Norw.:* Optison; *NZ:* Definity; *Pol.:* Luminity†; *Port.:* Luminity†; Optison; *Spain:* Luminity†; *Swed.:* Luminity†; Optison; *UK:* Luminity†; Optison; *USA:* Definity; Optison.

Pharmacopoeial Preparations

USP 36: Perflutren Protein-Type A Microspheres Injectable Suspension.

Propyliodone (rINN)

Propiliodona; Propyliodonum; Propyljodon; Propyylijodoni; Пропилиодон.

Propyl 1,4-dihydro-3,5-di-iodo-4-oxo-1-pyridylacetate.

$C_{10}H_{11}I_2NO_3$=447.0

CAS — 587-61-1.

ATC — V08AD03.

ATC Vet — QV08AD03.

UNII — 5NPJ6BPX36.

Description. Propyliodone contains about 56.8% of I.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Propyliodone). A white or almost white, crystalline powder. Is odourless or has a faint odour. Practically insoluble in water; soluble in alcohol, in acetone, and in ether. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Propyliodone is an iodinated radiographic contrast medium (p. 1580.1) that has been used for bronchography as either an aqueous or oily suspension.

Preparations

Pharmacopoeial Preparations

USP 36: Propyliodone Injectable Oil Suspension.

Sodium Tyropanoate (BAN, rINN)

Natrii Tyropanoas; NSC-107434; Tiropanoato de sodio; Tyropanoate de Sodium; Tyropanoate Sodium (USAN); Win-8851-2; Натрия Тиропаноат.

Sodium 2-(3-butyramido-2,4,6-tri-iodobenzyl)butyrate.

$C_{15}H_{17}I_3NNaO_3$=663.0

CAS — 27293-82-9 (tyropanoic acid); 7246-21-1 (sodium tyropanoate).

ATC — V08AC09.

ATC Vet — QV08AC09.

UNII — XRJ0P5FAYO.

Description. Sodium tyropanoate contains about 57.4% of I.

Profile

Sodium tyropanoate is an ionic monomeric iodinated radiographic contrast medium (p. 1580.1) with actions similar to those of iopanoic acid (p. 1591.1) and has been used for cholecystography and cholangiography.

Sulfur Hexafluoride (USAN)

BRI; Hexafluouro de azufre; Sulphur Fluoride; Sulphur Hexafluoride; Серы Гексафторид.

F_6S=146.1

CAS — 2551-62-4.

ATC — V08DA05.

ATC Vet — QV08DA05.

UNII — WS7LR311D6.

Profile

Sulfur hexafluoride is a gas with little biological activity that is used as an ultrasound contrast medium (p. 1580.2) for imaging of the blood vessels and for echocardiography. Microbubbles of sulfur hexafluoride are formed on reconstitution of the preparation and provide echo-enhancement; phospholipids and surfactants are included to stabilise the microbubbles. It is given intravenously as a suspension containing 45 micrograms/mL, in a usual dose of 2 mL for echocardiography, or 2.4 mL for imaging blood vessels; the dose may be repeated once if necessary.

Sulfur hexafluoride has been associated with hypersensitivity reactions; patients should be monitored for at least 30 minutes after use, and resuscitation equipment should be available. Particular care is advised in patients with ischaemic heart disease, in whom serious and occasionally fatal cardiac events have occurred: sulfur hexafluoride is contra-indicated in patients with recent acute coronary syndrome or clinically unstable ischaemic heart disease. It should also not be given to patients with severe pulmonary hypertension, uncontrolled hyper-

tension, acute respiratory distress syndrome, or right-to-left shunts. Care is advised in patients with lung disorders.

Sulfur hexafluoride has also been used as an adjunct in eye surgery for retinal detachment.

References.
1. Kim SS, *et al.* Outcomes of sulfur hexafluoride (SF6) versus perfluoropropane (C3F8) gas tamponade for macular hole surgery. *Retina* 2008; 28: 1408–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfur hexafluoride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 18/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: SonoVue; *Belg.*: SonoVue; *China*: SonoVue (声诺维); *Cz.*: SonoVue; *Denm.*: SonoVue; *Fin.*: SonoVue; *Fr.*: SonoVue; *Gr.*: SonoVue; *Hung.*: SonoVue; *Irl.*: SonoVue; *Ital.*: SonoVue; *Neth.*: SonoVue; *Norw.*: SonoVue; *Pol.*: SonoVue; *Port.*: SonoVue; *Singapore*: SonoVue; *Spain*: SonoVue; *Swed.*: SonoVue; *Switz.*: SonoVue; *UK*: SonoVue.

Table 1. Guide to potencies of topical corticosteroids.

Very potent	Potent	Moderately potent	Mild
Clobetasol propionate 0.05%	Amcinonide 0.1%	Alclometasone dipropionate 0.05%	Fluocinolone acetonide 0.0025%
Diflucortolone valerate 0.3%	Beclometasone dipropionate 0.025%	Betamethasone valerate 0.025%	Hydrocortisone 0.5% and 1%
Fluocinolone acetonide 0.2%	Betamethasone benzoate 0.025%	Clobetasone butyrate 0.05%	Hydrocortisone acetate 1%
Halcinonide 0.1%	Betamethasone dipropionate 0.05%	Desonide 0.05%	Methylprednisolone acetate 0.25%
Ulobetasol propionate 0.05%	Betamethasone valerate 0.1%	Desoximetasone 0.05%	
	Budesonide 0.025%	Fludroxycortide 0.0125%	
	Desoximetasone 0.25%	Flumetasone pivalate 0.02%	
	Diflorasone diacetate 0.05%	Fluocinolone acetonide 0.00625% and 0.01%	
	Diflucortolone valerate 0.1%	Fluocortin butyl 0.75%	
	Fluclorolone acetonide 0.025%	Fluocortolone preparations (caproate with pivalate, each 0.1%	
	Fluocinolone acetonide 0.025%	and caproate with either free alcohol or pivalate, each 0.25%)	
	Fluocinonide 0.05%	Hydrocortisone aceponate 0.1%	
	Fluprednidene acetate 0.1%	Hydrocortisone buteprate 0.1%	
	Fluticasone propionate 0.005% and 0.05%	Prednicarbate 0.25%	
	Hydrocortisone butyrate 0.1%		
	Methyprednisolone aceponate 0.1%		
	Mometasone furoate 0.1%		
	Triamcinolone acetonide 0.1%		

inflammation associated with rheumatoid and juvenile idiopathic arthritis, crystal arthropathies such as gout, and osteoarthritis can be alleviated by injection of a suitable corticosteroid, and in some cases the benefits may be quite prolonged. The longer-acting esters methylprednisolone acetate, triamcinolone acetonide, and triamcinolone hexacetonide are generally preferred. In some cases these may be combined with a local anaesthetic and a short-acting soluble corticosteroid for more rapid relief and to reduce the risk of a post-injection flare.

The risks associated with this technique have been reviewed.[5] Accurate injection technique is essential, and vigorous skin cleansing and an aseptic technique are required to avoid the introduction of infection into the joint; pre-existing joint infection is a contra-indication to corticosteroid injection. Intra-articular injections may be repeated if necessary but it has been suggested that a single joint should not be injected more than 3 or 4 times a year.

Periarticular injection is also used in various soft tissue disorders such as bursitis, capsulitis (painful shoulder syndromes), epicondylitis, tenosynovitis, and carpal tunnel syndrome. Particular care is required to avoid injection directly into a tendon, as this may cause the tendon to rupture. A shorter-acting corticosteroid such as hydrocortisone acetate may be more suitable for extra-articular lesions.

1. Anonymous. Articular and periarticular corticosteroid injections. *Drug Ther Bull* 1995; 33: 67–70.
2. Caldwell JR. Intra-articular corticosteroids: guide to selection and indications for use. *Drugs* 1996; 52: 507–14.
3. Pullar T. Routes of drug administration: intra-articular route. *Prescribers' J* 1998; 38: 123–6.
4. Schumacher HR, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. *Am J Med* 2005; 118: 1208–14.
5. Hunter JA, Blyth TH. A risk-benefit assessment of intra-articular corticosteroids in rheumatic disorders. *Drug Safety* 1999; 21: 353–65.

Intranasal route. In the management of allergic rhinitis corticosteroids are given intranasally in order to deliver the drug directly to the affected area, to use lower doses than are needed orally, and reduce the risk of systemic adverse effects. They are usually given by metered dose pump spray. The extent of local effect versus systemic effect may be influenced by the drug's molecular weight, lipophilicity, metabolism in nasal tissue, and type of delivery device.[1] In practice, however, when intranasal corticosteroid sprays are used as recommended there is little evidence that they have a significant systemic effect, and their local adverse effects are similar.[2,3] For details of systemic effects associated with inappropriately prolonged use of corticosteroid nasal drops, see Intranasal Administration under Precautions, p. 1619.1.

1. Lipworth BJ, Jackson CM. Safety of inhaled and intranasal corticosteroids: lessons for the new millennium. *Drug Safety* 2000; 23: 11–33.
2. Waddell AN, *et al.* Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J Laryngol Otol* 2003; 117: 843–5.
3. Meltzer EO. Intranasal steroids: managing allergic rhinitis and tailoring treatment to patient preference. *Allergy Asthma Proc* 2005; 26: 445–51.

Surgery. In the light of what was known in 1994 about the adrenal stress response to surgery, a discussion on the appropriate glucocorticoid supplementation for patients receiving corticosteroids who undergo surgery concluded that some recommendations were excessive.[1] (At this time in the UK recommended regimens consisted of the equivalent of 100 mg of hydrocortisone, usually as the sodium succinate, intravenously or intramuscularly before surgery, repeated every 8 hours, with the dose being tapered over 5 days to 20 or 30 mg daily.) It was suggested that for minor surgery 25 mg of hydrocortisone or its equivalent pre-operatively was adequate; where surgical stress was likely to be moderate, 50 to 75 mg of hydrocortisone or its equivalent daily in divided doses for 1 to 2 days was suggested. For major surgical stress, a target of 100 to 150 mg of hydrocortisone or its equivalent should be given daily in divided doses for 2 to 3 days, although less might be given if the patient's pre-operative glucocorticoid dose was low. It was also considered that the practice of gradually reducing postoperative coverage over several days was not supported by evidence except in cases of high-dose glucocorticoid use for prolonged periods.

Another review[2] of this subject also concluded that for minor surgery, 25 mg of hydrocortisone, or the patient's usual dose of corticosteroid, given pre-operatively, was appropriate. However, the authors argued that for surgery causing greater stress, it was preferable to avoid the increases in plasma-cortisol associated with intermittent bolus doses. They suggested that for moderate surgery an intravenous dose of hydrocortisone 25 mg at induction should be followed by an infusion of 100 mg over 24 hours; for major surgery the infusion should be continued for 48 to 72 hours after surgery. The usual oral corticosteroid dose may be resumed once these infusions have been completed, providing the postoperative course is uncomplicated and gastrointestinal function has returned.

A subsequent systematic review[3] found that there was still little data from controlled studies of this common practice. Based on this limited information, it was concluded that patients being treated with therapeutic doses of corticosteroids would not routinely need additional stress doses when undergoing surgical procedures, provided they were given their usual daily dose of corticosteroid. However, they should be monitored carefully in the perioperative period, and stress doses of hydrocortisone may be needed in patients with volume-refractory hypotension; a serum-cortisol measurement was recommended in these patients before starting therapy. Patients receiving physiological replacement doses of corticosteroids for primary disease of the hypothalamic-pituitary-adrenal axis would require supplemental corticosteroid doses in the perioperative period.

For currently recommended regimens see Uses and Administration of Hydrocortisone, p. 1640.3.

1. Salem M, *et al.* Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg* 1994; 219: 416–25.
2. Nicholson G, *et al.* Peri-operative steroid supplementation. *Anaesthesia* 1998; 53: 1091–1104.
3. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Arch Surg* 2008; 143: 1222–6.

Topical application. Guidelines[1,2] for the correct use of topical corticosteroids recommend that an appropriately potent preparation to bring the skin disorder under control should be used. Some recommend use of the lowest potency that will control the disorder, while others have advocated starting treatment with a more potent preparation, treatment may then be continued with a less potent preparation and with less frequent application, once control is obtained. The most potent topical corticosteroids are generally reserved for recalcitrant dermatoses. Once the skin has healed, treatment should be tailed off. Particular care is necessary in the use of topical corticosteroids in children, and the more potent preparations are contra-indicated in infants under 1 year of age, although potent preparations may be needed briefly in older children. It has been suggested that a 'steroid holiday' of at least 2 weeks be considered in children after each 2 or 3 weeks of daily topical therapy to allow thinned epidermis to restore itself and maintain its barrier function.[3]

Care is also necessary in applying corticosteroids to certain anatomical sites such as the face and flexures; some advocate using only hydrocortisone 0.5 or 1% on the face. Advice should be given that topical corticosteroids should be applied sparingly in thin layers, by smoothing gently into the skin preferably after a bath, and that no benefit is gained from more frequent than twice daily application or by vigorous rubbing.

In a study to determine the requirement of topical corticosteroids,[4] 16 adult patients with eczema were treated with a variety of topical preparations until substantial clearing had occurred (up to 10 days). Results indicated that the mean requirement of preparation, regardless of potency or vehicle, was 6.86 g/m^2. Using this value the calculated quantities of topical corticosteroid to the nearest 5 g required for twice daily application for one week for the whole body, arms and legs only, and trunk only respectively were as follows:

- 6 months of age, 35 g, 20 g, and 15 g
- 1 year, 45 g, 25 g, and 15 g
- 4 years, 60 g, 35 g, and 20 g
- 8 years, 90 g, 50 g, and 35 g
- 12 years, 120 g, 65 g, and 45 g
- 16 years, 155 g, 85 g, and 55 g
- adult (70-kg male), 170 g, 90 g, and 60 g

Calculated quantities for the same application schedule for an adult (70-kg male) for individual portions of the body were:

- face and neck, 10 g
- one arm, 15 g
- one leg, 30 g
- hands and feet, 10 g

Table 1 (above) is a guide to the potency of topical corticosteroids. There may be some degree of overlap between these groups and, not surprisingly, there are minor variations to this classification. For example, some authorities consider fluocinolone acetonide 0.2% to be potent rather than very potent and halcinonide 0.1% to be potent rather than very potent.

It has been suggested, however, that the advent of nonfluorinated double esters such as hydrocortisone and methylprednisolone aceponates, or prednicarbate, has resulted in corticosteroids whose topical anti-inflammatory potency is not as closely related to their potential atrophic effects on skin, and that a classification taking both into account would be desirable.[5,6]

1. Miller JA, Munro DD. Topical corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 1980; 19: 119–34.
2. Savin JA. Some guidelines to the use of topical corticosteroids. *BMJ* 1985; 290: 1607–8.
3. Hepburn D, *et al.* Topical steroid holiday. *Pediatrics* 1995; 95: 455.
4. Maurice PDL, Saihan EM. Topical steroid requirement in inflammatory skin conditions. *Br J Clin Pract* 1985; 39: 441–2.
5. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; 10: 406–12.
6. Schäfer-Korting M, *et al.* Topical glucocorticoids with improved risk-benefit ratio: rationale of a new concept. *Drug Safety* 1996; 14: 375–85.

Acute respiratory distress syndrome

Acute respiratory distress syndrome (ARDS) is characterised by areas of lung damage leading to decreased pulmonary compliance, pulmonary oedema associated with increased capillary and alveolar permeability, and refractory hypoxaemia. Diffuse pulmonary infiltrates are seen on radiography, and patients have dyspnoea, tachypnoea, or both. Diagnosis is mainly clinical, and there has been some disagreement as to what should be included in the syndrome;[1] it is now seen as forming the most severe end of a spectrum of symptoms due to lung inflammation and increased permeability known as acute lung injury.[1-3] ARDS is sometimes considered to refer to 'adult respiratory distress syndrome' but it is not confined to adult patients.[1,2]

ARDS may be caused by a variety of pulmonary or systemic insults but is particularly frequent in patients with

sepsis;[4] because of an association with failure of other organs it has been suggested that it represents the pulmonary component of multiple organ failure syndrome.[5] Many inflammatory mediators have been implicated in its pathogenesis but evidence suggests that recruitment of neutrophils by interleukins plays an important role.[1]

Management. Therapy for ARDS is essentially supportive. Mechanical ventilation is necessary in most cases, and circulatory support may require fluids, cardiac inotropes, and vasodilators. Optimum management may include diuretics and fluid restriction provided that cardiac output and oxygen delivery are maintained.[6] Because of the association with sepsis antibacterial therapy may be important, but studies of anti-endotoxin antibodies have produced disappointing results.[3] Improvements in supportive care and mechanical ventilation are considered to have reduced the mortality rate.[1,7] Partial liquid ventilation with perfluorocarbons has been tried, but good evidence to support this intervention is not available.[8]

Many drugs have been proposed for the management of ARDS, but, although case reports are often encouraging, none has been conclusively shown to improve mortality in controlled studies,[9] or in systematic review.[10] Corticosteroids do not appear to reduce acute mortality,[3,5] and may increase mortality rates in persistent ARDS if started 14 or more days after the onset of the condition.[11] Good results have been reported with inhaled epoprostenol,[12,13] but these results await confirmation from larger controlled studies.

There is evidence that ketoconazole may prevent development of ARDS in patients considered at risk,[14,15] but it does not appear to be effective as a treatment for ARDS or acute lung injury.[16] Among the drugs that have proved disappointing are acetylcysteine,[17,18] alprostadil,[19,20] and nitric oxide[21] (which may, however, improve oxygenation to some degree). Studies[22,23] of pulmonary surfactants in ARDS have generally shown no survival benefit; however, calfactant significantly decreased mortality when given to infants, children, and adolescents.[24]

A high-fat, low-carbohydrate diet has been advocated for patients with ARDS. Supplementation with eicosapentaenoic acid and gamolenic acid has been reported to benefit oxygenation, but with no significant effect on mortality.[7,25]

1. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1334–49. Correction. *ibid.*; 343: 520.
2. Bernard GR, *et al.* The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149: 818–24.
3. Bigatello LM, Zapol WM. New approaches to acute lung injury. *Br J Anaesth* 1996; 77: 99–109.
4. Plantadosi CA, Schwartz DA. The acute respiratory distress syndrome. *Ann Intern Med* 2004; 141: 460–70.
5. Weinberger SE. Recent advances in pulmonary medicine (part 2). *N Engl J Med* 1993; 328: 1462–70.
6. Elsasser S, *et al.* Adjunctive drug treatment in severe hypoxic respiratory failure. *Drugs* 1999; 58: 429–46.
7. Hite RD, Morris PE. Acute respiratory distress syndrome: pharmacological treatment options in development. *Drugs* 2001; 61: 897–907.
8. Davies MW, Fraser JF. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
9. Jain R, DalNogare A. Pharmacological therapy for acute respiratory distress syndrome. *Mayo Clin Proc* 2006; 81: 205–12.
10. Adhikari N, *et al.* Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 05/05/05).
11. Steinberg KP, *et al.* National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 2006; 354: 1671–84.
12. Walmrath D, *et al.* Aerosolised prostacyclin in adult respiratory distress syndrome. *Lancet* 1993; 342: 961–2.
13. Walmrath D, *et al.* Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 1996; 153: 991–6.
14. Yu M, Tomasa G. A double-blind, prospective, randomized trial of ketoconazole, a thromboxane synthetase inhibitor, in the prophylaxis of the adult respiratory distress syndrome. *Crit Care Med* 1993; 21: 1635–42.
15. Sinuff T, *et al.* Development, implementation, and evaluation of a ketoconazole practice guideline for ARDS prophylaxis. *J Crit Care* 1999; 14: 1–6.
16. The ARDS Network Authors. Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2000; 283: 1995–2002.
17. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; 20: 918–23.
18. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; 12: 177–82.
19. Bone RC, *et al.* Randomized double-blind, multicenter study of prostaglandin E_1 in patients with the adult respiratory distress syndrome. *Chest* 1989; 96: 114–19.
20. Abraham E, *et al.* Liposomal prostaglandin E_1 in acute respiratory distress syndrome: a placebo-controlled, randomized, double-blind, multicenter clinical trial. *Crit Care Med* 1996; 24: 10–15.
21. Sokol J, *et al.* Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 05/05/05).
22. Anzueto A, *et al.* Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. *N Engl J Med* 1996; 334: 1417–21.
23. Spragg RG, *et al.* Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med* 2004; 351: 884–92.
24. Wilkon DF, *et al.* Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA* 2005; 293: 470–6. Correction. *ibid.*; 294: 900.
25. Cranshaw J, *et al.* The pulmonary physician in critical care 9: non-ventilatory strategies in ARDS. *Thorax* 2002; 57: 823–9.

Adrenal hyperplasia, congenital

See Congenital Adrenal Hyperplasia, p. 1603.2.

Adrenocortical insufficiency

The major function of the adrenal cortex is the production of glucocorticoid and mineralocorticoid hormones, of which cortisol (hydrocortisone) and aldosterone respectively are the most important. Glucocorticoid production is regulated by the hypothalamic-pituitary-adrenal axis, being stimulated by the release of ACTH (adrenocorticotrophic hormone; corticotropin) from the pituitary, while mineralocorticoid production is mainly controlled by the renin-angiotensin system.

Adrenocortical insufficiency is defined as inadequate production of endogenous corticosteroids. It may be primary (Addison's disease), due to destruction of the adrenal cortex; or secondary, due to hypothalamic or pituitary disease, or corticosteroid therapy which suppresses ACTH release.[1,2] Diagnosis can be difficult, even with the aid of hormone tests such as the tetracosactide stimulation test.[3]

Clinical manifestations of adrenocortical insufficiency are usually seen once about 90% of the adrenal cortex is destroyed. Weight loss, anorexia, weakness, and fatigue may be accompanied by gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhoea, as well as electrolyte abnormalities (hyponatraemia, hyperkalaemia), salt craving, and orthostatic hypotension. In acute cases, abdominal pain and rigidity, fever, volume depletion, hypotension, and shock may occur. Hyperpigmentation, especially of skin creases, exposed areas, and scars is a distinguishing feature of primary, but not secondary, insufficiency. Hypoglycaemia is more likely in secondary deficiency due to lack of growth hormone, and failure of other pituitary hormones usually accompanies secondary adrenocortical insufficiency.

Treatment for acute insufficiency should be with intravenous hydrocortisone as the sodium succinate, sodium phosphate or other readily soluble ester: the usual dose is the equivalent of 100 mg every 6 to 8 hours for 24 hours. Volume depletion, dehydration, hypotension and hypoglycaemia should be corrected with intravenous saline and glucose, and precipitating factors, such as infection, should be dealt with appropriately. Provided no complications occur, the dosage of hydrocortisone can be tapered over 4 or 5 days to oral maintenance therapy.

For chronic insufficiency the usual oral dosage of **maintenance or replacement therapy** is hydrocortisone 20 to 30 mg, preferably divided unequally, e.g. 30 mg as 20 mg in the morning and 10 mg in the evening, in an attempt to mimic the natural pattern of secretion. Other corticosteroids have been used, including cortisone acetate, prednisolone, prednisone, and dexamethasone, but offer no advantage over hydrocortisone. Patients with primary insufficiency also require additional mineralocorticoid replacement with fludrocortisone, usually in a dose of 100 micrograms daily. Mineralocorticoid replacement is not usually necessary in secondary insufficiency. There has been some evidence of benefit from studies of adjunctive oral use of prasterone, another steroidal compound secreted by the adrenal glands, in patients with primary or secondary adrenal insufficiency.

Corticosteroid cover. An increase in replacement therapy is required during periods of stress. In mild infection, a doubling of the maintenance dose of hydrocortisone may be appropriate but for major infection, or severe stress such as surgery, parenteral therapy is required. It is generally considered safer to overestimate rather than underestimate the appropriate cover. For regimens used to provide cover in patients with secondary insufficiency due to corticosteroid therapy see Uses and Administration of Hydrocortisone, p. 1640.3.

1. Arit W, Allolio B. Adrenal insufficiency. *Lancet* 2003; 361: 1881–93.
2. Chakera AJ, Vaidya B. Addison disease in adults: diagnosis and management. *Am J Med* 2010; 123: 409–13.
3. Dorin RI, *et al.* Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; 139: 194–204.

AIDS

For the use of corticosteroids in AIDS patients with pneumocystis pneumonia, see p. 1610.2.

Alopecia

The management of alopecia (p. 1682.3) is often difficult. In alopecia areata intralesional corticosteroids, most commonly triamcinolone, will induce hair growth although they are not suitable when more than 50% of the scalp is involved.[1] Regrowth is confined to the site of injection and therefore patchy, although soon concealed by spontaneous growth from uninjected regions. Some atrophy of the scalp is inevitable. Topical corticosteroids are mostly reported to be ineffective although some consider them beneficial; the use of systemic corticosteroids is controversial, given their adverse effects and a lack of evidence that they alter the long-term prognosis.

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; 61: 53–69.

Anaemias

For the use of corticosteroids in haemolytic anaemias, including cold haemagglutinin disease, see p. 1122.2.

Anaphylaxis

Anaphylaxis (p. 1293.2) is a medical emergency and prompt treatment with adrenaline is required. Corticosteroids have little place in the immediate management of anaphylaxis since their beneficial effects are delayed for several hours. However, in severely ill patients early use of intramuscular or slow intravenous hydrocortisone may avert late sequelae and help prevent or shorten protracted reactions, although it is doubtful whether they prevent biphasic attacks. Corticosteroids may be particularly useful in patients with an asthmatic component.

Aspiration syndromes

For a review of the management of aspiration syndromes, including reference to the probable lack of value of corticosteroids, see p. 1804.2.

Asthma

The cornerstones of current asthma therapy, as discussed in more detail on p. 1195.2, are the $beta_2$-adrenoceptor agonists and the corticosteroids. Drug therapy for **chronic asthma** is managed by a stepwise approach. Patients requiring only occasional relief from symptoms may be managed with an inhaled short-acting $beta_2$ agonist as required. An inhaled corticosteroid such as beclometasone dipropionate, budesonide, or fluticasone may be added to therapy if symptomatic relief is needed more than three times a week but regular use is important since corticosteroids take several hours to exert an effect in asthma. If control is still inadequate, a long-acting $beta_2$ agonist is added. The dose of inhaled corticosteroid may be increased if further control is needed, and other additional therapies include anti-leukotrienes or theophylline. Severe asthma requires regular bronchodilator therapy as well as high-dose inhaled corticosteroids, while in the most severe cases, regular oral corticosteroids may also be required. A short 'rescue' course of oral corticosteroid may be needed at any stage for an acute exacerbation. Corticosteroids should be used cautiously in children because of possible adverse effects on growth.

Guidelines vary slightly in their definition of low, moderate and high inhaled corticosteroid doses. In *UK* guidelines,[1] the reference inhaled corticosteroid was beclometasone dipropionate (p. 1621.2) given via a chlorofluorocarbon (CFC)-containing metered-dose inhaler (MDI) as this is the formulation used in most of the evidence-base that supports current asthma management. However, CFC-containing MDIs are being phased out and adjustments to doses may be required for other formulations and corticosteroids. Differences in CFC-free beclometasone dipropionate formulations available in the UK mean they are not dose equivalent (see Reformulation, under Beclometasone Dipropionate, p. 1622.3).

- For **adults**, doses in the range 200 to 800 micrograms daily of beclometasone dipropionate or equivalent are considered *low* initial doses, with 400 micrograms daily being an appropriate starting dose for most patients
- a dose of 800 micrograms daily is considered *moderate*
- doses greater than 800 up to 2000 micrograms daily are *high*
- For **children** aged 5 to 12 years, doses in the range 200 to 400 micrograms daily are considered *low* initial doses, with 200 micrograms daily being an appropriate starting dose for most patients
- a dose of 400 micrograms daily is considered *moderate*
- doses over 400 up to 800 micrograms daily are *high*

The definition in *global* guidelines[2] vary slightly.

- For **adults**, doses in the range 200 to 500 micrograms daily of beclometasone dipropionate via a CFC-containing MDI are considered *low* initial doses
- doses over 500 up to 1000 micrograms daily are considered *moderate*
- doses over 1000 up to 2000 micrograms daily are *high*
- For **children** aged over 5 years, doses in the range 100 to 200 micrograms daily are considered *low* initial doses
- doses over 200 up to 400 micrograms daily are considered *moderate*
- doses over 400 micrograms daily are *high*

In the *USA* CFC-containing beclometasone dipropionate MDIs have been phased out and replaced with MDIs containing hydrofluoroalkane (HFA). The recommended US dose of beclometasone dipropionate HFA MDI, relative to a CFC-containing MDI formulation, is lower due to differences in delivery characteristics between the products; however, a definitive comparative therapeutic ratio has not been found. In addition, doses are given as the amount delivered *from* the mouthpiece in the USA, instead of the amount delivered *into* the mouthpiece. For one product, Qvar (*Teva, USA*), each 100 micrograms of beclometasone dipropionate delivered *into* the mouthpiece equates to 80 micrograms delivered *from* the mouthpiece. Doses in the US guidelines[3] will therefore seem somewhat lower, although in practical terms there is probably little difference.

- For **adults**, US guidelines consider doses in the range 80 to 240 micrograms daily of beclometasone dipropionate via a HFA-containing MDI to be *low* initial doses
- doses greater than 240 up to 480 micrograms daily are considered *moderate*
- doses above 480 micrograms daily are *high*
- For **children** aged 5 to 12 years, doses in the range 80 to 160 micrograms daily are considered *low* initial doses
- doses greater than 160 up to 320 micrograms daily are considered *moderate*
- doses above 320 micrograms daily are considered *high*

Acute severe asthma (status asthmaticus) is potentially life-threatening and is treated with inhaled oxygen and $beta_2$ agonists, as well as systemic corticosteroids; inhaled ipratropium bromide, and intravenous magnesium sulfate, xanthine, or $beta_2$ agonist may need to be added. Once lung function is stabilised the patient can be discharged on a regimen of oral and inhaled corticosteroids, and bronchodilators.

1. Scottish Intercollegiate Guidelines Network/The British Thoracic Society. British guideline on the management of asthma: a national clinical guideline. May 2008, revised June 2009. Available at: http://www.sign.ac.uk/pdf/sign101.pdf (accessed 06/08/09)
2. Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2009. Available at: http://www.ginasthma.com/download.asp?intId=411 (accessed 12/04/10)
3. National Asthma Education and Prevention Program. *Expert Panel Report 3: guidelines for the diagnosis and management of asthma*. Bethesda: National Heart, Lung, and Blood Institute, 2007. Available at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf (accessed 16/11/07)

Behçet's syndrome

Behçet's syndrome (or Behçet's disease) is a recurrent multifocal disorder most prevalent in the Far East and countries of the Mediterranean and Middle East.

The clinical features include oral and genital ulceration, skin lesions, arthritis, vasculitis leading to thromboembolic disorders and aneurysms, ocular lesions (including uveitis, hypopyon, and iridocyclitis leading eventually to blindness), and CNS involvement (meningomyelitis, dementia, extrapyramidal symptoms, and paralysis, sometimes fatal). Gastrointestinal disturbances and involvement of other body systems have been reported. However, the complete gamut of symptoms is unlikely in a single patient, and the disease has been classified into mucocutaneous, arthritic, neurological, and ocular forms depending on the predominant symptoms. Diagnosis can be difficult, but oral ulceration, with recurrent genital ulceration, ocular involvement, and skin lesions or a positive pathergy test are considered the major diagnostic criteria.[1,2]

Treatment of Behçet's syndrome is essentially symptomatic and empirical. Controlled studies are mostly lacking, which has hindered meta-analysis.[3] Where possible, topical treatment of **mucocutaneous** lesions should be attempted before embarking on systemic therapy. Topical application of a potent corticosteroid, such as triamcinolone acetonide, or a tetracycline solution may be tried for oral ulceration.[1,2] Genital ulcers can be treated topically with betamethasone ointment.[2] Sucralfate suspension used topically has also been reported to be effective in oral and genital ulceration,[4] and topical mesalazine has been tried.[5] Systemically, colchicine is reportedly beneficial in the treatment of mucocutaneous lesions,[1,2] although a review failed to find any evidence of benefit from colchicine treatment.[3] Systemic corticosteroids are advocated for severe mucocutaneous disease;[4] oral prednisolone has been given for erythema nodosum.[1,2] Thalidomide is also effective for mucocutaneous symptoms,[2,4] although relapses occur on cessation of therapy. Other drugs with reported efficacy for mucocutaneous symptoms include azathioprine,[4] benzathine benzylpenicillin (sometimes with colchicine),[4] dapsone,[1,2,4,6] interferon alfa,[4,6] levamisole,[4] pentoxifylline,[1] and rebamipide.[4,6]

The use of NSAIDs in the treatment of **arthritis** in patients with Behçet's disease is controversial,[4] although indometacin is used.[2] Colchicine is also used,[2,4] and sulfasalazine may be beneficial in patients who do not respond to NSAIDs.[1] Corticosteroids used with azathioprine are effective,[2,4] as are interferon alfa,[1,2,4] and benzathine benzylpenicillin.[3]

Short courses of intravenous methylprednisolone or high-dose oral prednisolone with subsequent tapering are used in the acute phase of **neurological** involvement, and may be followed by chlorambucil, cyclophosphamide, or methotrexate.[2] Chronic CNS disease is generally resistant to therapy.[2]

Ocular involvement in Behçet's disease leads to blindness in about a quarter of patients.[1,2] For acute attacks of anterior uveitis, topical mydriatics such as tropicamide, or corticosteroid drops may be sufficient. Local injections of corticosteroids are used to treat acute attacks of posterior uveitis, and systemic use may also be required.[2] Oral corticosteroid therapy does not improve visual prognosis, however, and may lead to secondary retinal thrombosis or cataracts;[2] good evidence of its benefit is lacking.[3] Colchicine is used for prophylaxis of both anterior and posterior uveitis;[2] ciclosporin is considered more effective at controlling acute ocular attacks[1] but its efficacy appears to gradually decline.[2,4] Other drugs deemed effective in preventing ocular inflammation include azathioprine,[1-4] chlorambucil,[2,4] and cyclophosphamide.[2,4] There are reports of benefit with benzathine benzylpenicillin, interferon alfa, levamisole, methotrexate, pentoxifylline, sulfasalazine, and thalidomide.[4] Tacrolimus has also been beneficial in cases of refractory uveitis.[1,4] Combinations of the above drugs are also used, such as corticosteroids with immunosuppressants, or corticosteroids with cytotoxics.[4]

In patients with **vasculitis**, arteritis is treated with systemic corticosteroids and cyclophosphamide, either orally or pulsed monthly boluses.[1,2] Deep-vein thrombosis has been treated with anticoagulants, such as warfarin or heparin, but caution is advised in those with pulmonary arteritis because of the risk of potentially fatal haemoptysis,[2] and their use is generally not recommended.[1,4] Aspirin is used with immunosuppressants, particularly azathioprine.[4] Stanozolol has also been used to treat the vascular symptoms of Behçet's disease.

Corticosteroids and sulfasalazine are the main drugs used for **gastrointestinal** lesions;[2] thalidomide has also been beneficial.[1]

Infliximab has been found to reduce acute ocular inflammation,[7] and heal gastrointestinal ulceration;[8] it has also proved effective in controlling neurological manifestations of the disease.[9]

1. Kaklamani VG, *et al.* Behçet's disease. *Semin Arthritis Rheum* 1998; 27: 197–217.
2. Sakane T, *et al.* Behçet's disease. *N Engl J Med* 1999; 341: 1284–91.
3. Saenz A, *et al.* Pharmacotherapy for Behçet's syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 22/08/08).
4. Kaklamani VG, Kaklamanis PG. Treatment of Behçet's disease—an update. *Semin Arthritis Rheum* 2001; 30: 299–312. Correction. *ibid.*; 31: 69.
5. Ranzi T, *et al.* Successful treatment of genital and oral ulceration in Behcet's disease with topical 5-aminosalicylic acid (5-ASA). *Br J Dermatol* 1989; 120: 471–2.
6. Yurdakul S, *et al.* Behçet syndrome. *Curr Opin Rheumatol* 2004; 16: 38–42.
7. Sfikakis PP, *et al.* Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet* 2001; 358: 295–6.
8. Travis SPL, *et al.* Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor α antibody. *Gut* 2001; 49: 725–8.
9. Ribi C, *et al.* Efficacy of TNF α blockade in cyclophosphamide resistant neuro-Behçet disease. *J Neurol Neurosurg Psychiatry* 2005; 76: 1733–5.

Bell's palsy

Bell's palsy is a condition that may be caused[1,2] by herpes simplex virus 1. It affects the facial nerves and results in facial muscle weakness and paralysis. It is often accompanied by pain and lachrymation. Untreated, over 80% of all patients recover completely or almost so, while in a smaller number facial weakness persists; complete failure of motor recovery is very rare.

Corticosteroids dramatically relieve pain associated with Bell's palsy,[3] and their use in treatment is widely accepted.[4] A meta-analysis has confirmed that early corticosteroid treatment increases the frequency of full recovery of facial motor function.[5] A short course of oral therapy is usually given, such as prednisolone 25 mg twice daily for 10 days starting within 72 hours of the onset of symptoms.[6]

It has been suggested that aciclovir or valaciclovir might be effective in treating Bell's palsy. However, systematic reviews and meta-analyses have found them to be of no benefit when given alone.[7,8] Reviews of studies that added these antivirals to corticosteroid therapy have found either no additional benefit[9] or a reduction in risk of unsatisfactory recovery of only borderline significance.[7]

1. Murakami S, *et al.* Bell palsy and herpes simplex virus: identification of viral DNA in endoneurial fluid and muscle. *Ann Intern Med* 1996; 124: 27–30.
2. Gilden DH. Bell's palsy. *N Engl J Med* 2004; 351: 1323–31.
3. Adour KK. Current concepts in neurology: diagnosis and management of facial paralysis. *N Engl J Med* 1982; 307: 348–51.
4. Knox GW. Treatment controversies in Bell palsy. *Arch Otolaryngol Head Neck Surg* 1998; 124: 821–3.
5. Salinas RA, *et al.* Corticosteroids for Bell's palsy (idiopathic facial paralysis). Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 15/04/10).
6. Madhok V, *et al.* Prescribe prednisolone alone for Bell's palsy diagnosed within 72 hours of symptom onset. *BMJ* 2009; 338: 410–11.
7. de Almeida JR, *et al.* Combined corticosteroid and antiviral treatment for Bell palsy: a systematic review and meta-analysis. *JAMA* 2009; 302: 985–93.
8. Lockhart P, *et al.* Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 15/04/10).
9. Quant EC, *et al.* The benefits of steroids versus steroids plus antivirals for treatment of Bell's palsy: a meta-analysis. *BMJ* 2009; 339: b3354.

Bites and stings

Corticosteroids (prednisone 100 mg daily) have been recommended for the stabilisation of erythrocyte membranes in the management of systemic envenomation by the brown recluse spider (*Loxosceles reclusa*).[1] They have also been given after stings by some species of scorpion, although their value is not certain.[1] Corticosteroids are considered to have no place in snake venom poisoning.[2] Topical corticosteroids may be useful for mild itching of healing skin after some types of jelly fish sting, while systemic corticosteroids have been used for delayed hypersensitivity reactions.[3]

1. Binder LS. Acute arthropod envenomation: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; 4: 163–73.
2. Nelson BK. Snake envenomation: incidence, clinical presentation and management. *Med Toxicol* 1989; 4: 17–31.
3. Penner PJ, Williamson JA. Worldwide deaths and severe envenomation from jelly fish stings. *Med J Aust* 1996; 165: 658–61.

Bone cysts

Intralesional corticosteroid injection (usually methylprednisolone) has been used as an alternative to surgical or other methods for the treatment of bone cysts.[1-6] An early report indicated that methylprednisolone acetate 40 to 200 mg injected into unicameral bone cysts under brief general anaesthesia stimulated bone formation to obliterate the cyst or promoted sufficient healing to prevent further fractures.[1] A single injection was sufficient for healing in 10 to 25% of cysts; only rarely were more than 4 injections needed. Treatment of an aneurysmal bone cyst with methylprednisolone and calcitonin has also been reported.[7] (Systemic corticosteroids are, of course, generally associated with bone loss rather than bone formation—see Effects on the Bones and Joints, p. 1616.2).

1. Weinert CR. Administering steroids in unicameral bone cysts. *West J Med* 1989; 150: 684–5.
2. Rud B, *et al.* Simple bone cysts in children treated with methylprednisolone acetate. *Orthopedics* 1991; 14: 185–7.
3. Goel AR, *et al.* Unicameral bone cysts: treatment with methylprednisone acetate injections. *J Foot Ankle Surg* 1994; 33: 6–15.
4. Parsch K, *et al.* Die juvenile Knochenzyste: Steilenwert und Therapieergebnisse der Kortisoninjektion. *Orthopade* 1995; 24: 65–72.
5. Hasheml-Nejad A, Cole WG. Incomplete healing of simple bone cysts after steroid injections. *J Bone Joint Surg Br* 1997; 79: 727–30.
6. Journeau P, Ciotlos D. Place de l'embrochage centro-médullaire et de l'injection de corticoïdes dans le traitement des kystes osseux essentiels de l'enfant. *Rev Chir Orthop Reparatrice Appar Mot* 2003; 89: 333–7.
7. Gladden ML, *et al.* Aneurysmal bone cyst of the first cervical vertebrae in a child treated with percutaneous intralesional injection of calcitonin and methylprednisolone: a case report. *Spine* 2000; 25: 527–30.

Brain injury

See Spinal Cord and Head Injury, p. 1613.2.

Bronchiolitis

Acute bronchiolitis is usually caused by RSV infection (p. 961.3) in infants and young children, and may contribute to the subsequent development of asthma. Supportive therapy, where necessary, may involve the use of oxygen and bronchodilators (see also p. 1221.2). Many studies have failed to show a benefit from corticosteroid therapy, and it has generally been considered that corticosteroids have no role in the management of the condition.[1] Although one study did find that oral prednisolone might be of benefit,[2] it was suggested that the results might be due to inclusion of children with asthma among the study population.[3] A systematic review[4] found little benefit in terms of length of hospital stay or admission rate and no evidence of improvement in clinical scores, respiratory rate, or oxygen saturation when compared with placebo. However, a study[5] found that a 3-day course of oral prednisolone given to children aged 6 to 35 months with respiratory distress reduced disease severity, length of hospital stay, and the duration of symptoms. Inhaled corticosteroids seem to be of little value[6] and a systematic review concluded that they did not prevent post-bronchiolitic wheezing when given during the initial acute phase of bronchiolitis.[7]

1. Fitzgerald DA, Kilham HA. Bronchiolitis: assessment and evidence-based management. *Med J Aust* 2004; 180: 399–404.
2. van Woensel JBM, *et al.* Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997; 52: 634–7.
3. Milner AD. The role of corticosteroids in bronchiolitis and croup. *Thorax* 1997; 52: 595–7.
4. Patel H, *et al.* Glucocorticoids for acute viral bronchiolitis in infants and young children [withdrawn and awaiting update]. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 22/08/08).
5. Csonka P, *et al.* Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway

disease: a randomized, placebo-controlled trial. *J Pediatr* 2003; 143: 725–30.
6. Richter H, Seddon P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. *J Pediatr* 1998; 132: 849–53.
7. Blom D, *et al.* Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 26/02/08).

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia is the major cause of chronic lung disease (defined as the need for supplementary oxygen more than 28 days after birth) in neonates. It has also been defined as oxygen dependency beyond a corrected gestational age of 36 weeks.[1] It is considered to comprise 4 radiographically distinct stages, of which stage 1 is effectively indistinguishable from neonatal respiratory distress syndrome (see p. 1608.3), with which it is usually associated. A 'bubbly' appearance of the lung is seen in radiographs of advanced disease. Bronchopulmonary dysplasia is invariably associated with prolonged mechanical ventilation, but it is uncertain whether it plays a causative role, or whether the disease develops anyway in infants with respiratory failure severe enough to need prolonged ventilation.[2] Other risk factors include prematurity, low birth-weight, pulmonary oedema, inflammation due to infection or other causes, and adrenal insufficiency.[1]

Treatment. Corticosteroids, usually in the form of systemic dexamethasone, have been widely used in premature infants with bronchopulmonary dysplasia,[1] or who are considered to be at high risk of it (the borderline between treatment and prophylaxis in studies in these mechanically ventilated infants is not always clear[3]). Dexamethasone has been reported to improve pulmonary outcome, allowing more rapid weaning from mechanical ventilation, and in some studies was reported to improve neurological outcome as well.[4] However, some investigators consider its benefits in the long term inadequately established.[3,5,6]

There also remains some concern about possible adverse effects of dexamethasone, especially on long-term development.[1,7,8] One meta-analysis suggested that use was associated with a high incidence of cerebral palsy and neurodevelopmental impairment, and should be abandoned.[9] Infants requiring mechanical ventilation and given intravenous dexamethasone or placebo in a study were followed up about 8 years later. Children in the dexamethasone group were shorter, had smaller head circumferences, poorer motor skills and coordination, lower IQ scores, and a higher frequency of clinically significant disabilities.[10] However, a 15-year follow-up of preterm infants given dexamethasone at 2 weeks of age, showed that those given a 42-day course had significantly better neurological outcomes than those given an 18-day course, or saline placebo.[11]

Many studies have favoured an initial dexamethasone dose of 500 micrograms/kg daily intravenously, tapered over a period of days to weeks, but it is not always clear if this is expressed in terms of the base or one of its esters,[12] and in any case regimens have varied between studies. Despite suggestions that starting therapy shortly after birth might minimise lung injury, evidence suggests that early therapy offers no advantage,[6,13] and may be more hazardous.[6,8,14–16] Meta-analysis has suggested that while beginning dexamethasone at any time between birth and 14 days of age reduced the risk of chronic lung disease, mortality was only reduced in the group who began treatment between 7 and 14 days of age.[17] However, a subsequent systematic review concluded that the benefits of therapy started between 7 to 14 days may not outweigh the adverse effects.[14]

In an attempt to propose guidelines, a review of the available evidence concluded that there was no role for corticosteroid use in the first 4 days of life and that use should be limited to exceptional clinical circumstances such as ventilator dependency in an infant after the second week of life. When used, the lowest effective dose was recommended for the shortest possible duration; dexamethasone 200 micrograms/kg daily (in two divided doses) for 3 days, then 100 micrograms/kg daily for 3 days, then 50 micrograms/kg daily for 3 days was suggested.[1]

Inhaled corticosteroids have also been investigated. A systematic review did not find any reduction in the incidence of chronic lung disease or the need for systemic corticosteroids.[18] Another systematic review of controlled studies found that inhaled corticosteroids may improve the rate of extubation in infants.[19]

Additional therapy is essentially supportive, including fluid restriction, nutritional supplementation, bronchodilators, and diuretics. Routine use of bronchodilators for prevention of bronchopulmonary dysplasia is not recommended, and studies of use in treatment are limited.[2] UK guidelines (issued in 1998 but not subsequently updated) considered that diuretics were indicated for episodes of associated cardiac failure but their long-term value was uncertain; if used, consideration should be given to a calcium-sparing regimen.[20] Improved pulmonary status has been reported with furosemide in established dysplasia,[21,22] although routine or sustained use cannot be recommended at present. Results with hydrochlorothiazide and spironolactone are more ambiguous.[23,24] Anaemia in infants with bronchopulmonary dysplasia has benefited from erythropoietin.[25] Although vitamin A deficiency has been implicated in the pathogenesis of bronchopulmonary dysplasia, studies of vitamin A supplementation have produced conflicting results. However, differences in patient population, postnatal therapies, and dosage of vitamin A could explain these results,[26] and some recommend supplementation to reduce the incidence of chronic lung disease.[2,26] Despite promising preliminary results,[27] treatment with alpha$_1$-proteinase inhibitor has not been shown to reduce the incidence of chronic lung disease.[2] Similarly, although there is evidence suggesting that early use of sudismase may reduce development of chronic lung disease (but not bronchopulmonary dysplasia),[28] routine use is not recommended.[2]

1. Grier DG, Halliday HL. Management of bronchopulmonary dysplasia in infants: guidelines for corticosteroid use. *Drugs* 2005; 65: 15–29.
2. Shah PS. Current perspectives on the prevention and management of chronic lung disease in preterm infants. *Pediatr Drugs* 2003; 5: 463–80.
3. Kari MA, *et al.* Dexamethasone treatment in preterm infants at risk for bronchopulmonary dysplasia. *Arch Dis Child* 1993; 68: 566–9.
4. Cummings JJ, *et al.* A controlled trial of dexamethasone therapy in preterm infants with bronchopulmonary dysplasia. *N Engl J Med* 1989; 320: 1505–10.
5. Jones R, *et al.* Controlled trial of dexamethasone in neonatal chronic lung disease: a 3-year follow-up. *Pediatrics* 1995; 96: 897–906.
6. Papile L-A, *et al.* A multicenter trial of two dexamethasone regimens in ventilator-dependent premature infants. *N Engl J Med* 1998; 338: 1112–18.
7. Greenough A. Gains and losses from dexamethasone for neonatal chronic lung disease. *Lancet* 1998; 352: 835–6.
8. American Academy of Pediatrics Committee on Fetus and Newborn, Canadian Paediatric Society Fetus and Newborn Committee. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. *Pediatrics* 2002; 109: 330–8. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics;109/2/330 (accessed 27/04/04)
9. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. Available at: http://www.biomedcentral.com/1471-2431/1/1 (accessed 27/04/04)
10. Yeh TF, *et al.* Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N Engl J Med* 2004; 350: 1304–13.
11. Gross SJ, *et al.* Follow-up at 15 years of preterm infants from a controlled trial of moderately early dexamethasone for the prevention of chronic lung disease. *Pediatrics* 2005; 115: 681–7.
12. Jones RAK, Grant AM. The "dose" question. *Pediatrics* 1992; 90: 781.
13. Tapia JL, *et al.* The effect of early dexamethasone administration on bronchopulmonary dysplasia in preterm infants with respiratory distress syndrome. *J Pediatr* 1998; 132: 48–52.
14. Halliday HL, *et al.* Moderately early (7-14 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 12/05/05).
15. The Vermont Oxford Network Steroid Study Group. Early postnatal dexamethasone therapy for the prevention of chronic lung disease. *Pediatrics* 2001; 108: 741–8.
16. Halliday HL, *et al.* Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2010 (accessed 26/04/10).
17. Bhuta T, Ohlsson A. Systematic review and meta-analysis of early postnatal dexamethasone for prevention of chronic lung disease. *Arch Dis Child Fetal Neonatal Ed* 1998; 79: F26–F33.
18. Shah V, *et al.* Early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birth weight preterm neonates. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 25/04/08).
19. Lister P, *et al.* Inhaled steroids for neonatal chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 12/05/05).
20. Report of the second working group of the British Association of Perinatal Medicine. Guidelines for good practice in the management of neonatal respiratory distress syndrome. Guideline produced in November 1998, not valid beyond 2002. Available at: http://www.bapm.org/media/documents/publications/rds.pdf (accessed 15/08/05)
21. Brion LP, *et al.* Aerosolized diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 22/08/08).
22. Brion LP, Primhak RA. Intravenous or enteral loop diuretics for preterm infants with (or developing) chronic lung disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 12/05/05).
23. Engelhardt B, *et al.* Effect of spironolactone-hydrochlorothiazide on lung function in infants with chronic bronchopulmonary dysplasia. *J Pediatr* 1989; 114: 619–24.
24. Albersheim SG, *et al.* Randomized, double-blind, controlled trial of long-term diuretic therapy for bronchopulmonary dysplasia. *J Pediatr* 1989; 115: 615–20.
25. Ohls RK, *et al.* A randomized double-blind, placebo-controlled trial of recombinant erythropoietin in treatment of the anemia of bronchopulmonary dysplasia. *J Pediatr* 1993; 123: 996–1000.
26. Shenai JP. Vitamin A supplementation in very low birth weight neonates: rationale and evidence. *Pediatrics* 1999; 104: 1369–74.
27. Stiskal JA, *et al.* α_1-Proteinase inhibitor therapy for the prevention of chronic lung disease of prematurity: a randomized, controlled trial. *Pediatrics* 1998; 101: 89–94.
28. Davis JM, *et al.* Pulmonary outcome at 1 year corrected age in premature infants treated at birth with recombinant human CuZn superoxide dismutase. *Pediatrics* 2003; 111: 469–76.

Cachexia

For mention of the use of corticosteroids in cancer-related cachexia see under Uses and Administration of Megestrol, p. 2289.3.

Cardiac arrhythmias

Atrial fibrillation (see Cardiac Arrhythmias, p. 1266.1) is common after cardiothoracic surgery, and although it is usually self-limiting, it may be associated with increased morbidity and mortality. Cardiopulmonary bypass used during surgery provokes an inflammatory response that may contribute to atrial fibrillation, and there has been some investigation of the effect of prophylactic corticosteroids. Dexamethasone, hydrocortisone, methylprednisolone, and prednisolone have been tried, in single doses or short courses; studies have been small and results mixed.[1–3] A systematic review[3] of 9 studies found that corticosteroids may reduce the incidence of atrial fibrillation and shorten hospital stay, but the effect may depend on the dose, and larger studies are required.

1. Yared J-P, *et al.* Effect of dexamethasone on atrial fibrillation after cardiac surgery: prospective, randomized, double-blind, placebo-controlled trial. *J Cardiothorac Vasc Anesth* 2007; 21: 68–75.
2. Halonen J, *et al.* Corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. *JAMA* 2007; 297: 1562–7.
3. Baker WL, *et al.* Effect of perioperative corticosteroid use on the incidence of postcardiothoracic surgery atrial fibrillation and length of stay. *Heart Rhythm* 2007; 4: 461–8.

Cerebral oedema

Corticosteroids (usually dexamethasone) play an important role in the treatment of cerebral oedema caused by malignancy and dexamethasone is advocated for the cerebral oedema associated with high-altitude disorders (see p. 1276.2). The management of raised intracranial pressure and the usual drugs used to treat it are discussed on p. 1271.3.

Corticosteroids have also been used for the management of raised intracranial pressure in patients with head injuries or stroke, but despite earlier small studies showing them to be beneficial in some patients, current opinion is that corticosteroids are not useful in head injuries (see Spinal Cord and Head Injury, p. 1613.2) or stroke, and that their adverse effects may outweigh any possible benefit.

Chronic active hepatitis

Chronic hepatitis is characterised by liver cell necrosis and inflammation that persists for more than 6 to 12 months. Probably the most serious form is chronic active hepatitis in which inflammatory infiltrates (mononuclear and plasma cells) are found within and around the portal areas, with piecemeal necrosis of adjacent liver cells, and in severe cases bands of necrotic tissue between portal tracts or to the central vein (bridging necrosis). Symptoms are essentially non-specific and include fatigue, malaise, fever, anorexia, jaundice, and raised serum aminotransferase values; biopsy is required for accurate diagnosis. The causes of chronic active hepatitis vary and may include: infection with hepatitis viruses; adverse effects of drugs such as isoniazid, methyldopa, or nitrofurantoin; or, particularly in women, an apparently idiopathic form, auto-immune hepatitis.

Treatment with corticosteroids is widely used in patients with auto-immune hepatitis.[1,2] A moderate initial oral dose of 20 to 30 mg of prednisolone or prednisone daily or a higher dose of 60 mg daily may be used,[3–5] and is then slowly tapered over several months to the minimum required for maintenance. Daily maintenance therapy appears more effective than alternate-day regimens. Patients who respond (as shown by a return of serum aminotransferase values to the normal or near normal range and a reduction in the inflammatory processes on biopsy) usually require prolonged treatment; although some patients remain in remission for months to years after withdrawal, relapse generally occurs, and therapy should be reinstated when the disease becomes active again.[1]

Combined treatment including azathioprine is frequently given and may be the preferred initial treatment in some patients;[4,5] such treatment is at least as effective as a corticosteroid alone,[2] can produce[6,7] and maintain[8,9] remission, and permits a reduction in corticosteroid dosage in a group of patients who will require long-term drug treatment.[1] There has been some dispute about the value of azathioprine alone, but combined therapy has generally been found to be superior.[6] However, azathioprine has been used alone in high doses to maintain remission.[5,9]

In contrast to the fairly extensive experience with azathioprine, ciclosporin is little used in this condition; once started it appears to be required indefinitely.[4] It may be an alternative in severe disease where corticosteroids alone or with azathioprine cannot suffice. Mycophenolate mofetil may offer an alternative to azathioprine.[5] Some investiga-

tors have also used cyclophosphamide successfully,[3] and tacrolimus has been reported to be of benefit.[10]

Penicillamine has been tried as an alternative to prolonged use of corticosteroid maintenance therapy, the dose of penicillamine being gradually increased over several months to a suitable maintenance dose as the dosage of corticosteroid is tapered off.

It is generally agreed that immunosuppression is not suitable in patients with viral chronic active hepatitis.[11] However, combination therapy has been reported to produce benefit in patients positive for HBsAg,[6] and it has been reported[12] that patients with chronic active hepatitis of unknown cause, at least some of whom may have hepatitis C,[11] respond as well to corticosteroids or combined therapy as patients with proven auto-immune disease. Liver transplantation (p. 1936.3) may be necessary in patients who are refractory to or intolerant of immunosuppressive therapy, and in whom end-stage liver disease develops.[1]

1. Krawitt EL. Autoimmune hepatitis. *N Engl J Med* 2006; 334: 54–66.
2. Stavinoha MW, Soloway RD. Current therapy of chronic liver disease. *Drugs* 1990; 39: 814–40.
3. Meyer zum Büschenfelde K-H, Lohse AW. Autoimmune hepatitis. *N Engl J Med* 1995; 333: 1004–5.
4. Czaja AJ. Drug therapy in the management of type 1 autoimmune hepatitis. *Drugs* 1999; 57: 49–68.
5. Al-Khalidi JA, Czaja AJ. Current concepts in the diagnosis, pathogenesis, and treatment of autoimmune hepatitis. *Mayo Clin Proc* 2001; 76: 1237–52.
6. Giusti G, *et al.* Immunosuppressive therapy in chronic active hepatitis (CAH): a multicentric retrospective study on 867 patients. *Hepatogastroenterology* 1984; 31: 24–9.
7. Vegnente A, *et al.* Duration of chronic active hepatitis and the development of cirrhosis. *Arch Dis Child* 1984; 59: 330–5.
8. Stellon AJ, *et al.* Randomised controlled trial of azathioprine withdrawal in autoimmune chronic active hepatitis. *Lancet* 1985; i: 668–70.
9. Johnson PJ, *et al.* Azathioprine for long-term maintenance of remission in autoimmune hepatitis. *N Engl J Med* 1995; 333: 958–63.
10. Van Thiel DH, *et al.* Tacrolimus: a potential new treatment for autoimmune chrohic active hepatitis: results of an open-label preliminary trial. *Am J Gastroenterol* 1995; 90: 771–6.
11. Gitnick G. Cryptogenic versus autoimmune chronic hepatitis: to split or to lump? *Mayo Clin Proc* 1990; 65: 119–21.
12. Czaja AJ, *et al.* Clinical features and prognostic implications of severe corticosteroid-treated cryptogenic chronic active hepatitis. *Mayo Clin Proc* 1990; 65: 23–30.

Chronic obstructive pulmonary disease

Corticosteroids play some part in the symptomatic and palliative management of chronic obstructive pulmonary disease (COPD—p. 1199.1). Inhaled corticosteroids can reduce exacerbation rates, although their effect on long-term outcome is less clear. There has also been some concern about increased rates of pneumonia reported in patients treated with inhaled corticosteroids. Guidelines on the management of COPD generally recommend that regular treatment with inhaled corticosteroids should be combined with a long-acting $beta_2$ agonist for symptomatic patients with moderate to severe disease and repeated exacerbations. Short courses of systemic corticosteroids may be used in the management of acute exacerbations of COPD.

Churg-Strauss syndrome

The Churg-Strauss syndrome is sometimes classified with polyarteritis nodosa (see p. 1610.2), although, unlike the latter, pulmonary manifestations are relatively common in Churg-Strauss syndrome. Patients commonly have a history of allergic disease (rhinitis, sinusitis, and asthma); intractable asthma and eosinophilia with granulomatous vasculitis characterise the syndrome.

Treatment is similar to that of polyarteritis nodosa, being based on systemic corticosteroids and, where necessary, cyclophosphamide.[1-4] When cyclophosphamide is used, intravenous pulse therapy is often preferred to continuous oral dosage,[2,4] as it has been shown to reduce adverse effects and allows for a lower total dose.[3,4] Substitution of cyclophosphamide with azathioprine or mycophenolate mofetil after 4 to 6 months can also allow for reduced overall doses of cyclophosphamide to be given,[3,4] although azathioprine is not as effective as cyclophosphamide for primary treatment.[3] In patients with haemorrhagic cystitis, there is some suggestion that mycophenolate mofetil may be more effective than azathioprine.[3] Interferon alfa may also be of benefit.[4,5] In patients refractory to corticosteroids and cyclophosphamide, there are reports of benefit with antilymphocyte immunoglobulins or intravenous immunoglobulins.[3]

1. Guillevin L, *et al.* Treatment of polyarteritis nodosa and Churg-Strauss syndrome: a meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. *Ann Med Interne (Paris)* 1992; 143: 405–16.
2. Guillevin L, Lhote F. Classification and management of necrotising vasculitides. *Drugs* 1997; 53: 805–16.
3. Conron M, Beynon HLC. Churg-Strauss syndrome. *Thorax* 2000; 55: 870–7.
4. Noth I, *et al.* Churg-Strauss syndrome. *Lancet* 2003; 361: 587–94.
5. Tatsis E, *et al.* Interferon-α treatment of four patients with the Churg-Strauss syndrome. *Ann Intern Med* 1998; 129: 370–4.

Cogan's syndrome

Corticosteroids are useful in the treatment of Cogan's syndrome, a condition characterised by non-syphilitic interstitial keratitis and audiovestibular symptoms including deafness.[1-3] The deafness, although often irreversible, may respond to systemic corticosteroids begun within 2 weeks of onset of symptoms (prednisolone or prednisone, at least 1.5 mg/kg daily for 2 weeks is advised) and ocular involvement benefits from topical corticosteroid therapy (e.g. prednisolone 1% at a rate of 1 drop every hour for 1 to 2 weeks).[3] Improvement in ocular symptoms has also been seen with sodium cromoglicate eye drops.[4] For patients with severe Cogan's syndrome including large-vessel vasculitis, corticosteroids have been used with other immunosuppressants such as azathioprine, ciclosporin and cyclophosphamide.[5] Methotrexate has also been tried.[6]

1. Anonymous. Cogan's syndrome. *Lancet* 1991; 337: 1011–12.
2. Vollertsen RS, *et al.* Cogan's syndrome: 18 cases and a review of the literature. *Mayo Clin Proc* 1986; 61: 344–61.
3. St Clair EW, McCallum RM. Cogan's syndrome. *Curr Opin Rheumatol* 1999; 11: 47–52.
4. Carter P, Nabarro J. Cromoglycate for Cogan's syndrome. *Lancet* 1987; i: 858.
5. Allen NB, *et al.* Use of immunosuppressive agents in the treatment of severe ocular and vascular manifestations of Cogan's syndrome. *Am J Med* 1990; 88: 296–301.
6. Riente L, *et al.* Efficacy of methotrexate in Cogan's syndrome. *J Rheumatol* 1996; 23: 1830–1.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia comprises a heterogeneous group of disorders due to inherited defects of steroid synthesis in the adrenal gland, the most frequent of which are defects involving 21-hydroxylase or 11-β-hydroxylase. Defective enzyme production blocks the formation of cortisol and aldosterone; the pituitary produces increased amounts of ACTH in an attempt to compensate, but this results in excessive adrenal androgen production. Presentation varies from virilisation and abnormal genital formation at birth to mild cryptic forms that may be detected only later in life. Salt-losing forms (due to lack of aldosterone or the accumulation of precursors with antagonist activity) may lead to hyperkalaemia, acidosis, and dehydration. Patients with 11-β-hydroxylase defect are also prone to hypertension.

Neonates with **salt-losing forms** of congenital adrenal hyperplasia require urgent treatment. Treatment usually consists of a mineralocorticoid, fludrocortisone, and a glucocorticoid (usually hydrocortisone) in regimens similar to those for adrenocortical insufficiency (see p. 1600.2).[1-5] Saline infusion or addition of salt to the feed is required initially.

Even where salt-losing symptoms are not overt or marked, control is reportedly better with a mineralocorticoid added to therapy, rather than with hydrocortisone alone,[4] and it has been recommended that children with salt-losing congenital adrenal hyperplasia should continue to receive combined therapy at least until adult life.[1] Careful titration of dosage is important to avoid growth retardation and toxicity, and potent synthetic glucocorticoids such as betamethasone and dexamethasone may be inappropriate in infants and children with the condition, even in the non-salt-losing form. An alternative approach is the use of flutamide and testolactone to block androgenic effects, with a reduced dose of hydrocortisone.[4,6] However, studies suggest that normal growth is possible with regular glucocorticoid therapy.[7,8]

Patients with **non-salt-losing congenital adrenal hyperplasia** may be adequately managed with glucocorticoids alone, and in mild late-onset forms a single dose daily in the late evening (when its suppressive effect on ACTH production is greatest) may be sufficient. In adults who do not require mineralocorticoid treatment betamethasone or dexamethasone may be useful because of their lack of mineralocorticoid actions.

Surgical correction may be necessary in females with masculinised external genitalia. Giving a glucocorticoid to pregnant women whose offspring are considered at risk has been tried in an attempt to prevent virilisation:[3] dexamethasone is preferred to hydrocortisone because of a lack of placental degradation.[4]

1. Griffiths KD, *et al.* Plasma renin activity in the management of congenital adrenal hyperplasia. *Arch Dis Child* 1984; 59: 360–5.
2. Young MC, Hughes IA. Response to treatment of congenital adrenal hyperplasia in infancy. *Arch Dis Child* 1990; 65: 441–4.
3. American Academy of Pediatrics. Technical report: congenital adrenal hyperplasia. *Pediatrics* 2000; 106: 1511–18. Correction. *ibid.* 2001; 107: 1450. [Re-affirmed May 2005] Also available at: http://aappolicy.aappublications.org/cgi/reprint/pediatrics;106/6/1511.pdf (accessed 26/08/08)
4. Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med* 2003; 349: 776–88.
5. Merke DP, Bornstein SR. Congenital adrenal hyperplasia. *Lancet* 2005; 365: 2125–36.
6. Merke DP, Cutler GB. New approaches to the treatment of congenital adrenal hyperplasia. *JAMA* 1997; 277: 1073–6.
7. Rivkees SA, Crawford JD. Dexamethasone treatment of virilizing congenital adrenal hyperplasia: the ability to achieve normal growth. *Pediatrics* 2000; 106: 767–73.
8. Eugster EA, *et al.* Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. *J Pediatr* 2001; 138: 26–32.

Corneal graft rejection

Corticosteroids are the mainstay of postoperative prophylaxis and treatment of corneal graft rejection.[1] Topical and subconjunctival corticosteroids are widely used, but in acute rejection episodes involving the endothelium systemic therapy is usually necessary. A single 500-mg intravenous pulse of methylprednisolone appears to be as effective as up to 2 weeks of treatment with oral prednisolone 60 to 80 mg daily for the management of severe endothelial rejection.[2] However, another study found that addition of a single intravenous pulse of 500 mg methylprednisolone to local corticosteroid treatment with betamethasone and dexamethasone gave no benefit over local therapy alone.[3]

In high-risk patients corticosteroids alone provide insufficient immunosuppression and systemic immunosuppression has been tried, although the evidence base is limited,[1] mainly relating to the use of ciclosporin, and with inconsistent results. Mycophenolate mofetil has also been tried,[1,4] and has been reported to be as effective as ciclosporin in preventing acute rejection after high-risk corneal transplantation.[4] However, because most patients are healthy and transplantation is not life-saving, the risks of systemic immunosuppression may be hard to justify.[1] Topical ciclosporin has also been investigated.[5]

Corticosteroids have also been used to reduce inflammation after corneal reconstruction using tissue engineered from autologous oral mucosal epithelium.[6]

For discussions of the role of corticosteroids in other forms of organ and tissue grafting, see Organ and Tissue Transplantation, p. 1932.2.

1. Coster DJ, Williams KA. The impact of corneal allograft rejection on the long-term outcome of corneal transplantation. *Am J Ophthalmol* 2005; 140: 1112–22.
2. Hill JC, *et al.* Corticosteroids in corneal graft rejection: oral versus single pulse therapy. *Ophthalmology* 1991; 98: 329–33.
3. Hudde T, *et al.* Randomised controlled trial of corticosteroid regimens in endothelial corneal allograft rejection. *Br J Ophthalmol* 1999; 83: 1348–52.
4. Reis A, *et al.* Mycophenolate mofetil versus cyclosporin A in high risk keratoplasty patients: a prospectively randomised clinical trial. *Br J Ophthalmol* 1999; 83: 1268–71.
5. Zhao J-C, Jin X-Y. Local therapy of corneal allograft rejection with cyclosporine. *Am J Ophthalmol* 1995; 19: 189–94.
6. Nishida K, *et al.* Corneal reconstruction with tissue-engineered cell sheets composed of autologous oral mucosal epithelium. *N Engl J Med* 2004; 351: 1187–96.

Croup

Croup is an acute childhood syndrome of upper respiratory tract inflammation (laryngotracheobronchitis) associated with viral infection, usually by parainfluenza virus although other viruses may also produce the syndrome. It is characterised by harsh, barking cough, stridor, and hoarseness, most usually occurring at night.[1-3]

Traditional home management has revolved around the inhalation of steam, despite a lack of evidence for efficacy, but symptoms may be sufficiently alarming to result in presentation to a hospital.

In severe croup there is clear evidence that treatment with a systemic corticosteroid reduces symptoms and decreases the need for intubation.[4-6] Oral dexamethasone is as effective as intramuscular,[7] and while dexamethasone 600 micrograms/kg is commonly prescribed, lower doses of 300 micrograms/kg and 150 micrograms/kg appear to be equally effective.[2] Nebulised budesonide has also been reported to be effective,[8-10] and of similar efficacy to inhalation of nebulised adrenaline.[11] However despite the theoretical attraction of this route, studies have failed to find any significant difference in efficacy between nebulised budesonide 2 mg and oral dexamethasone 600 micrograms/kg,[12] or combination therapy with both,[13] and another study found 600 micrograms/kg of dexamethasone given intramuscularly to be more effective than 4 mg of nebulised budesonide.[14] In contrast, others have found that addition of nebulised budesonide to oral dexamethasone produced more rapid improvement than the latter alone.[15] Studies have also shown a significant benefit from corticosteroids in children with mild to moderate croup,[12,16-18] and although the use of such potent drugs in children with a mild, largely self-limiting condition has been questioned,[19] a review of the risks and benefits concluded that oral dexamethasone 150 micrograms/kg, or nebulised budesonide 2 mg were the treatment of choice in mild to moderate croup while oral prednisolone 1 mg/kg should be given for croup requiring intubation.[1] However, nebulised adrenaline is probably the initial drug of choice where rapid relief of obstructive symptoms is required.[2,3] Oxygen is given to those children with upper airway obstruction and significant oxygen desaturation.[3] Heliox, a mixture of helium and oxygen, may be used as adjunctive therapy to

glucocorticoids, for short-term treatment of refractory croup.[2]

1. Yates RW, Doull IJM. A risk-benefit assessment of corticosteroids in the management of croup. *Drug Safety* 1997; 16: 48–55.
2. Brown JC. The management of croup. *Br Med Bull* 2002; 61: 189–202.
3. Fitzgerald DA, Kilham HA. Croup: assessment and evidence-based management. *Med J Aust* 2003; 179: 372–7.
4. Kairys SW, *et al.* Steroid treatment of laryngotracheitis: a meta-analysis of the evidence from randomized trials. *Pediatrics* 1989; 83: 683–93.
5. Preezer NJ, *et al.* Steroids in croup: do they increase the incidence of successful extubation? *Anaesth Intensive Care* 1990; 18: 224–8.
6. Geelhoed GC. Sixteen years of croup in a Western Australian teaching hospital: effects of routine steroid treatment. *Ann Emerg Med* 1996; 28: 621–6.
7. Rittichier KK, Ledwith CA. Outpatient treatment of moderate croup with dexamethasone: intramuscular versus oral dosing. *Pediatrics* 2000; 106: 1344–8.
8. Klassen TP, *et al.* Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994; 331: 285–9.
9. Husby S, *et al.* Treatment of croup with nebulised steroid (budesonide): a double blind, placebo controlled study. *Arch Dis Child* 1993; 68: 352–5.
10. Godden CW, *et al.* Double blind placebo controlled trial of nebulised budesonide for croup. *Arch Dis Child* 1997; 76: 155–8.
11. Fitzgerald D, *et al.* Nebulized budesonide is as effective as nebulized adrenaline in moderately severe croup. *Pediatrics* 1996; 97: 722–5.
12. Geelhoed GC, MacDonald WBG. Oral and inhaled steroids in croup: a randomized placebo-controlled trial. *Pediatr Pulmonol* 1995; 20: 355–61.
13. Klassen TP, *et al.* Nebulized budesonide and oral dexamethasone for treatment of croup: a randomized controlled trial. *JAMA* 1998; 279: 1629–32.
14. Johnson DW, *et al.* A comparison of nebulised budesonide, intramuscular dexamethasone, and placebo for moderately severe croup. *N Engl J Med* 1998; 339: 498–503.
15. Klassen TP, *et al.* The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996; 97: 463–6.
16. Geelhoed GC, *et al.* Efficacy of a small single dose of oral dexamethasone for outpatient croup: a double blind placebo controlled clinical trial. *BMJ* 1996; 313: 140–2.
17. Russell K, *et al.* Glucocorticoids for croup. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2004 (accessed 12/05/05).
18. Bjornson CL, *et al.* A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med* 2004; 351: 1306–13.
19. Macfarlane PI, Suri S. Steroids in the management of croup. *BMJ* 1996; 312: 510.

Cystic fibrosis

Corticosteroids have been used orally or by inhalation in the management of the inflammatory response of the lungs in cystic fibrosis (see p. 177.2) but do not form part of standard management.

Deafness

For references to the use of corticosteroids in the treatment of deafness associated with Cogan's syndrome, see p. 1603.2.

Dermatomyositis

For references to the treatment of dermatomyositis with corticosteroids, see Polymyositis and Dermatomyositis, p. 1611.1.

Eaton-Lambert myasthenic syndrome

Corticosteroids have been tried in the treatment of Eaton-Lambert myasthenic syndrome (p. 684.1).

Eczema

Topical corticosteroids have an important role in the management of atopic eczema (p. 1684.1). The least potent preparation that is effective should be used, combined with regular use of an emollient; in mild to moderate disease the topical corticosteroid is only given for 1 to 2 weeks at a time. Most patients with mild to moderate eczema respond to treatment with a mildly potent preparation such as 1% hydrocortisone ointment. For older children and adults with refractory disease, a more potent topical corticosteroid should be considered for long enough to bring the disease under control, followed by a weaker preparation as the condition improves.

The use of systemic corticosteroids is a treatment of last resort in resistant severe eczema, usually for short periods to control the disease, and very rarely for maintenance.

Eosinophilic oesophagitis

For mention of the use of corticosteroids in eosinophilic oesophagitis, see p. 1807.1.

Epidermolysis bullosa

High-dose oral corticosteroids may be tried to control blistering in severe forms of epidermolysis bullosa (p. 1684.3).

Epilepsy

Corticosteroids and corticotropin have been commonly used to treat **infantile spasms**, which are generally unresponsive to conventional antiepileptics. There is, however, limited evidence for the efficacy of oral corticosteroids.[1] Corticotropin appears to be effective for short-term treatment, and one study[2] indicated that high-dose corticotropin was preferable to prednisone, but the optimum dose and duration of therapy have not been determined.[1,3] In addition, corticotropin and corticosteroids are associated with frequent and severe adverse effects, and as discussed on p. 506.1, some now prefer newer antiepileptics such as vigabatrin. A short-term study of infants with spasms of non-tuberous sclerosis origin found that tetracosactide or prednisolone were superior to vigabatrin.[4] However, vigabatrin is preferred for the treatment of spasms due to tuberous sclerosis,[3,4] and data are insufficient for recommendations regarding the use of any drug to improve the long-term outcome of children with infantile spasms.[1,3]

1. Mackay MT, *et al.* Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. *Neurology* 2004; 62: 1668–81.
2. Baram TZ, *et al.* High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. *Pediatrics* 1996; 97: 375–9.
3. Gupta R, Appleton R. Corticosteroids in the management of the paediatric epilepsies. *Arch Dis Child* 2005; 90: 379–84.
4. Lux AL, *et al.* The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet* 2004; 364: 1773–8.

Erythema multiforme

In the management of erythema multiforme (p. 1684.3) systemic corticosteroids may be considered in severe reactions but there has been controversy about their value.

Giant cell arteritis

Giant cell arteritis (temporal arteritis; cranial arteritis) is a vasculitic disorder that is frequently associated with polymyalgia rheumatica (p. 1610.3). It occurs mainly in persons over 50 years of age of European, particularly Scandinavian, extraction and is more common in women than men. It is characterised by inflammatory, granulomatous lesions with giant mononuclear cell infiltrates affecting large and medium sized arteries, particularly those supplying the neck and extracranial structures of head and arms. Symptoms vary but may include headache, scalp tenderness, claudication of the jaw, swelling and absence of pulse in the temporal artery, fever, weight loss, malaise, anaemia, visual disturbances, and irreversible blindness. About a third of all patients also have polymyalgia rheumatica.

Treatment is with corticosteroids,[1-8] and early diagnosis and treatment is desirable to reduce the risk of sudden blindness. Most regimens have involved high initial doses of corticosteroid to control the disease followed by reduction to a maintenance dose, but both initial and maintenance doses have varied considerably. Oral prednisone or prednisolone 40 to 60 mg daily initially is generally considered adequate in uncomplicated cases without visual symptoms;[1,4-6] this can then be reduced gradually according to the patient's response. Some, however, recommend[2] lower initial doses of about 20 mg daily.

While it is suggested that patients presenting with visual symptoms should receive 80 mg daily or 1 mg/kg daily of prednisone or prednisolone,[2,7,8] some ophthalmologists[9] recommend that all patients with giant cell arteritis receive these doses, as visual loss may be sudden and profound. Initial 1-g doses of pulsed intravenous methylprednisolone have also been used.[3,5,7,9]

Maintenance treatment is usually required and while a small number require indefinite treatment, most patients should be able to stop treatment within 5 years; however, relapses are not uncommon.[8]

Because of the need for prolonged corticosteroid therapy, adverse effects are common,[8] and their management difficult. Azathioprine has been added to corticosteroid therapy for its modest 'steroid-sparing' effect,[10] whereas results with methotrexate have been conflicting.[4,6,11] Other immunosuppressants have been tried,[4,6] but are not routinely used. Dapsone has been reported to be of benefit, but its use is limited by haematological toxicity.[4] Infliximab has been tried.[7]

The prognosis is excellent in adequately-treated patients, as the life expectancy of patients with giant cell arteritis is the same as the general population.[12]

1. Swannell AJ. Polymyalgia rheumatica and temporal arteritis: diagnosis and management. *BMJ* 1997; 314: 1329–32.
2. Wilke WS. What is the appropriate initial dose of corticosteroids to treat giant cell arteritis? *Cleve Clin J Med* 2000; 67: 546–8.
3. Gurwood AS, Malloy KA. Giant cell arteritis. *Clin Exp Optom* 2002; 85: 19–26.
4. Barilla-LaBarca M-L, *et al.* Polymyalgia rheumatica/temporal arteritis: recent advances. *Curr Rheumatol Rep* 2002; 4: 39–46.
5. Salvarani C, *et al.* Polymyalgia rheumatica and giant-cell arteritis. *N Engl J Med* 2002; 347: 261–71.
6. Weyand CM, Goronzy JJ. Giant-cell arteritis and polymyalgia rheumatica. *Ann Intern Med* 2003; 139: 505–15.
7. Rahman W, Rahman FZ. Giant cell (temporal) arteritis: an overview and update. *Surv Ophthalmol* 2005; 50: 415–28.
8. Matteson EL, Bird HA. Polymyalgia rheumatica and giant cell arteritis. In: Adebajo A, ed. *ABC of rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 107–13.
9. Ferris J, Lamb R. Polymyalgia rheumatica and giant cell arteritis. *BMJ* 1995; 311: 455.
10. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double blind study. *Ann Rheum Dis* 1986; 45: 136–8.
11. Hernández-García C, *et al.* Methotrexate treatment in the management of giant cell arteritis. *Scand J Rheumatol* 1994; 23: 295–8.
12. Matteson EL, *et al.* Long-term survival of patients with giant cell arteritis in the American College of Rheumatology giant cell arteritis classification criteria cohort. *Am J Med* 1996; 100: 193–6.

Glomerular kidney disease

Glomerular disease accounts for a considerable proportion of all kidney disease. Various forms of primary glomerular disease (glomerulopathy) are known, and are discussed below; in addition, many systemic diseases (connective tissue disorders such as SLE as well as malignancy and conditions such as diabetes), may result in secondary glomerular disorders. Despite the various potential causes it is thought that many of these diseases act by common immunological mechanisms to damage the glomerulus, either by accumulation of antigen-antibody complexes (immune-complex nephritis) or more rarely by the formation of antibodies to the glomerular basement membrane (anti-GBM nephritis).[1]

Since the kidney can respond in only a limited number of ways to glomerular damage, certain common presentations are seen regardless of aetiology, including **acute glomerulonephritis** (acute nephritis syndrome), which is marked by haematuria and proteinuria of abrupt onset, usually with renal impairment (a decrease in glomerular filtration rate), salt and water retention, and hypertension; and the **nephrotic syndrome**, which is marked by severe proteinuria, hypoalbuminaemia, and oedema. Other, less dramatic presentations of glomerular disease are asymptomatic proteinuria or microscopic haematuria; alternatively, glomerular disease may be one of the many potential causes of chronic renal failure. Appropriate management of these conditions depends to a considerable extent on the underlying disease.

• MANAGEMENT OF PRIMARY GLOMERULAR DISEASE.

Minimal change nephropathy (MCN; minimal change disease). This condition occurs mainly in children, the highest incidence being at 2 to 4 years, and is the main cause of childhood nephrotic syndrome. It also accounts for about 20% of adult cases of nephrotic syndrome.[2] It is treated with a corticosteroid. Regimens vary somewhat but a suggested oral regimen for adults has been 60 mg prednisolone daily for 4 days, reduced to 40 mg daily until remission occurs (which in 90% of patients will be within 3 weeks) and then tapered off.[2] In children, initial doses of 60 mg/m^2 of prednisolone or prednisone daily have been used,[3] which may be given for 4 weeks before switching to 40 mg/m^2 given on alternate days for a further 4 weeks, and then tapered off.[4] Lower relapse rates have been reported with 60 mg/m^2 prednisone given daily for 6 weeks, followed by 40 mg/m^2 on alternate days for 6 weeks; this 12-week course may be preferable to the standard 8-week course.[3] A modification to the children's dose is to give 60 mg/m^2 of prednisolone daily until there is a response when the dose is reduced to 40 mg/m^2 on alternate days for the next 4 weeks. If there is no response within 4 weeks of treatment with the 60 mg/m^2 dose then the drug should be withdrawn and the child considered to be corticosteroid resistant.[5] A systematic review of treatment regimens found that children with their first episode of nephropathy should be treated with prednisone for at least 3 months, and possibly up to 7, to reduce the risk of relapse.[6]

Relapse is common and occurs in about 60% of cases; relapses usually respond to a further course of corticosteroids, but if a third relapse occurs cyclophosphamide 2 to 3 mg/kg daily for 8 to 12 weeks may be added to a course of corticosteroid therapy.[2,3] Deflazacort may also be effective in corticosteroid-sensitive patients who do not respond to prednisone.[6] Cytotoxics or immunosuppressants are reserved for frequently relapsing or corticosteroid-dependent cases because of their potential for severe toxicity, including carcinogenesis; cyclophosphamide appears to be preferred to chlorambucil because it is perceived as entailing a somewhat lower risk, although both are effective.[3,7] Ciclosporin has been used long-term to achieve and maintain remission, although renal biopsies are advised to screen for nephrotoxicity.[3,7] Levamisole has also been reported to be of benefit.[3,7]

Focal glomerulosclerosis. Focal glomerulosclerosis is a sclerosing lesion affecting parts of the glomeruli which occurs in some patients who otherwise have symptoms characteristic of minimal change nephropathy, and some authorities do not regard it as a distinct disease. It is common in abusers of diamorphine and has also been linked with the nephropathy that can occur in patients with AIDS. Treatment is similar to that for minimal change nephropathy but only about 20% of cases respond to corticosteroids; addition of a cytotoxic immunosuppressant such as cyclophosphamide may improve the prospect of

remission. Responses to ciclosporin have been seen in both adults and children with corticosteroid-resistant disease.[3,8] Prolonged treatment may be necessary and relapse is common when ciclosporin is stopped.[7] Tacrolimus has been reported to be successful after ciclosporin failure,[3,8] and mycophenolate mofetil has been tried with conflicting results.[8] High-dose pulsed methylprednisolone, given in a tapering schedule over 6 years, has been reported to show high response rates in focal glomerulosclerosis.[3] In patients who fail to respond, progression to renal failure may occur over several years, but renal transplantation may not be helpful as disease can recur in the transplanted kidney.

Membranous nephropathy (membranous glomerulonephritis). This is a disease mainly of adults, in whom it is the single most important cause of the nephrotic syndrome, accounting for about 50% of cases. It is characterised by diffuse thickening of the glomerular basement membrane after subepithelial deposition of immune complexes. The course of disease is variable and often slow, with some spontaneous remissions, which makes it difficult to show the benefits of treatment and the use of potentially toxic drugs difficult to justify. Cyclophosphamide or chlorambucil combined with a corticosteroid appear to produce some clinical improvement, and stabilisation of progressive disease, but corticosteroids alone do not appear to be of benefit.[9-11] Cyclophosphamide may be preferred as it seems to be better tolerated.[11] Ciclosporin is an alternative but therapy may need to be continued for 6 months or more before remission occurs[9,10] and a systematic review found it to be no better than placebo.[11] Other immunosuppressants under investigation in this condition include mycophenolate mofetil[10] and rituximab. Recent studies have also emphasised the control of blood pressure and proteinuria using ACE inhibitors and angiotensin II receptor antagonists.[10]

Mesangiocapillary glomerulonephritis (MCGN; membranoproliferative glomerulonephritis; MPGN). Mesangiocapillary glomerulonephritis comprises 2 separate diseases, known as type I and type II, which both occur in children and young adults and usually result in nephrotic syndrome, although about 20% of cases present with acute glomerulonephritis. Both forms show proliferation of mesangial cells and thickening of glomerular walls with formation of deposits (in type I disease due to immune complexes) in capillary walls and basement membranes. There is no established treatment regimen: some improvement or stabilisation of renal function may occur with corticosteroids and cytotoxic immunosuppressants, but about half of all patients develop end-stage renal failure within 15 to 20 years (type I disease) or 6 to 10 years (type II disease). Antiplatelet drugs and anticoagulants have also been tried but as with other therapies there is little evidence of benefit, and some centres do not recommend any specific therapy, although prednisolone and cyclophosphamide may be offered to those with a rapidly progressive course.[12]

IgA nephropathy (Berger's disease) is the commonest cause of primary glomerular disease, and is most common in young men. It results in focal, segmental proliferative glomerulonephritis associated with mesangial formation of immune deposits largely composed of IgA. The usual presentation is acute glomerulonephritis with gross haematuria, often during or just after viral upper-respiratory-tract infection. Some patients develop rapidly progressive disease similar to idiopathic rapidly progressive glomerulonephritis, with renal failure within 6 months, but in many others the syndrome is benign, and requires only observation. No form of therapy has been unequivocally shown to be of value, but control of associated hypertension, usually with ACE inhibitors, is considered important. Corticosteroids and cytotoxic immunosuppressants may be tried in severe rapidly progressive disease.[13-17] Promising results have been seen with the use of n-3 fatty acids from fish oil, and there are also reports of benefit with normal immunoglobulin, and mycophenolate mofetil.[16]

Idiopathic rapidly progressive glomerulonephritis (RPGN). Although rapidly progressive glomerulonephritis (crescentic glomerulonephritis) may be a feature of other forms of glomerular disease such as IgA nephropathy (see above) or Goodpasture's syndrome (see below) it also occurs in an idiopathic form. The disease is characterised by the formation of glomerular crescents associated with leakage of fibrin from damaged capillaries, and loss of renal function is very rapid, sometimes with renal failure within weeks. Oral corticosteroids are of little value alone, but pulsed intravenous methylprednisolone followed by oral prednisone or prednisone and cyclophosphamide over several months has produced some impressive responses;[18,19] an alternative is the use of intensive plasma exchange with a corticosteroid and cytotoxic immunosuppressants.[20] Controlled studies of these therapies are mostly lacking, although a small prospective study[21] found lymphocytapheresis to be more effective than pulsed methylprednisolone as an addition to prednisolone and cyclophosphamide therapy for reduction of glomerular injury.

Goodpasture's syndrome. Goodpasture's syndrome is a form of anti-GBM nephritis in which rapidly progressive glomerulonephritis is accompanied by pulmonary haemorrhage (because the antibody responsible for the renal symptoms also reacts with the membranes of the alveoli). It is a disease mainly of young males. Pulmonary haemorrhage responds to high dose oral prednisolone or prednisone, or pulsed intravenous methylprednisolone, but corticosteroids are of little value in controlling renal lesions, which requires vigorous plasma exchange therapy with corticosteroids and cyclophosphamide on a daily or alternate-day basis for several weeks, until antibody is no longer detectable and disease progression has halted; it is important to begin therapy before renal damage becomes irreversible.[22]

• MANAGEMENT OF SECONDARY GLOMERULAR DISEASE.

Post-infectious glomerulonephritis. The classical form of post-infectious glomerulonephritis is post-streptococcal glomerulonephritis, which produces an immune-complex-mediated acute glomerulonephritis, but glomerular disease may follow other bacterial infections, as well as protozoal infections such as malaria (malaria-associated nephrotic syndrome is familiar in endemic regions) and viral infections such as AIDS (see Focal Glomerulosclerosis, above). In most cases no additional treatment beyond appropriate management of infection and general supportive care is warranted, and corticosteroids and cytotoxic immunosuppressants are not generally used and may in some cases be harmful.[23] Nonetheless, delayed progressive renal disease may occur in a minority of patients, and has prompted efforts to treat.[22]

Other secondary glomerulopathies. Where glomerular disease is secondary to other diseases (connective tissue disorders such as SLE, the vasculitides, Henoch-Schönlein purpura, thrombotic thrombocytopenic purpura, or others such as rheumatoid arthritis, amyloidosis, neoplasia, sickle-cell disease, gout, or diabetes mellitus) most treatment is directed at the underlying disease. In addition, symptomatic management such as the use of sodium restriction for the oedema of nephrotic syndrome may be appropriate; diuretics should be used cautiously because of the risk of hypovolaemia.[24] Proteinuria of various causes may respond to the use of ACE inhibitors or NSAIDs,[2,24] although care is required in patients with renal artery stenosis or renal failure respectively. Associated hypertension and hypercholesterolaemia should be treated, and anticoagulants such as heparin may be required for associated coagulation disorders.[24] Renal toxicity can arise from various drug treatments and this should also be treated symptomatically.

1. Chadban SJ, Atkins RC. Glomerulonephritis. *Lancet* 2005; **365**: 1797–1806.
2. Boulton-Jones M. Management of nephrotic syndrome. *Prescribers' J* 1993; **33**: 96–102. Correction. *ibid.*; 176.
3. Eddy AA, Symons JM. Nephrotic syndrome in childhood. *Lancet* 2003; **362**: 629–39.
4. Hogg RJ, *et al.* Evaluation and management of proteinuria and nephrotic syndrome in children: recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on proteinuria, albuminuria, risk, assessment, detection, and elimination (PARADE). *Pediatrics* 2000; **105**: 1242–9.
5. Report of a Workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. Consensus statement on management and audit potential for steroid responsive nephrotic syndrome. *Arch Dis Child* 1994; **70**: 151–7.
6. Hodson EM, *et al.* Corticosteroid therapy for nephrotic syndrome in children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 22/08/08).
7. Abeyagunawardena A, *et al.* Immunosuppressive therapy of childhood idiopathic nephrotic syndrome. *Expert Opin Pharmacother* 2002; **3**: 513–19.
8. Ponticelli C, Passerini P. Alternative treatments for focal and segmental glomerular sclerosis. *Clin Nephrol* 2001; **55**: 345–8.
9. Ponticelli C, Passerini P. Treatment of membranous nephropathy. *Nephrol Dial Transplant* 2001; **16** (suppl 5): 8–10.
10. Kincaid-Smith P. Pharmacological management of membranous nephropathy. *Curr Opin Nephrol Hypertens* 2002; **11**: 149–54.
11. Schieppati A, *et al.* Immunosuppressive treatment for idiopathic membranous nephropathy in adults with nephrotic syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/05/05).
12. Mason PD, Pusey CD. Glomerulonephritis: diagnosis and treatment. *BMJ* 1994; **309**: 1557–63. Correction. *ibid.* 1995; **310**: 116.
13. Goumenos D, *et al.* Can immunosuppressive drugs slow the progression of IgA nephropathy? *Nephrol Dial Transplant* 1995; **10**: 1173–81.
14. Faedda R, *et al.* Immunosuppressive treatment of Berger's disease. *Clin Pharmacol Ther* 1996; **60**: 561–7.
15. Kobayashi Y, *et al.* Steroid therapy during the early stage of progressive IgA nephropathy: a 10-year follow-up study. *Nephron* 1996; **72**: 237–42.
16. Donadio JV, Grande JP. IgA nephropathy. *N Engl J Med* 2002; **347**: 738–48.
17. Pozzi C, *et al.* Corticosteroids in IgA nephropathy: a randomised controlled trial. *Lancet* 1999; **353**: 883–7.
18. Bolton WK, Sturgill BC. Methylprednisolone therapy for acute crescentic rapidly progressive glomerulonephritis. *Am J Nephrol* 1989; **9**: 368–75.
19. Bruns FJ, *et al.* Long-term follow-up of aggressively treated idiopathic rapidly progressive glomerulonephritis. *Am J Med* 1989; **86**: 400–6.
20. Gianviti A, *et al.* Retrospective study of plasma exchange in patients with idiopathic rapidly progressive glomerulonephritis and vasculitis. *Arch Dis Child* 1996; **75**: 186–90.
21. Furuta T, *et al.* Lymphocytapheresis to treat rapidly progressive glomerulonephritis: a randomised comparison with steroid-pulse treatment. *Lancet* 1998; **352**: 203–4.
22. Couser WG. Glomerulonephritis. *Lancet* 1999; **353**: 1509–15.
23. Adeniyi A, *et al.* A controlled trial of cyclophosphamide and azathioprine in Nigerian children with the nephrotic syndrome and poorly selective proteinuria. *Arch Dis Child* 1979; **54**: 204–7.
24. Robinson RF, *et al.* Management of nephrotic syndrome in children. *Pharmacotherapy* 2003; **23**: 1021–36.

Gout

Systemic corticosteroids have been used as a second-line alternative to NSAIDs or colchicine in the treatment of acute gout (p. 600.1). A systematic review including 3 small studies of intramuscular or oral corticosteroids found that the evidence of benefit was inconclusive, although there seemed to be few adverse effects from such short-term treatment.[1] Subsequently, the same group carried out a small comparative double-blind study of oral prednisolone or naproxen for 5 days in patients with confirmed gout,[2] which concluded that the drugs were equally effective, and suggested that corticosteroids might be considered as a first-line option.

1. Janssens HJ, *et al.* Systemic corticosteroids for acute gout. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 06/01/09).
2. Janssens HJEM, *et al.* Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 2008; **371**: 1854–60.

Graves' ophthalmopathy

Patients with moderate to severe ophthalmopathy as a result of hyperthyroidism (p. 2332.2) may be treated with corticosteroids or with orbital radiotherapy. There is evidence of a synergistic effect when these therapies are combined. If orbital radiotherapy is contra-indicated, glucocorticoids may be combined with ciclosporin. There is some suggestion that intravenous pulse therapy is more effective than oral glucocorticoids.[1] Giving a corticosteroid with radio-iodine therapy may prevent transient exacerbation of Graves' ophthalmopathy.[2]

1. Hart RH, Perros P. Glucocorticoids in the medical management of Graves' ophthalmopathy. *Minerva Endocrinol* 2003; **28**: 223–31.
2. Bartalena L, *et al.* Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. *N Engl J Med* 1998; **338**: 73–8.

Haemangioma

Haemangiomas are benign vascular neoplasms of the skin that may enlarge dramatically before regressing spontaneously. Although no treatment is normally required, occasional complications due to ocular or visceral involvement, or associated thrombocytopenia due to platelet trapping (the Kasabach-Merritt syndrome), may merit treatment, generally with corticosteroids. Oral prednisone or prednisolone is usually given; intravenous high-dose methylprednisolone has been used for life-threatening haemangiomas.[1] Response is variable.[1-3] Another common technique is intralesional injection of a mixture of triamcinolone with betamethasone.[4] There has been a report of 2 infants responding to vincristine after corticosteroids had failed.[5] Interferon alfa has been used for corticosteroid-refractory lesions.[1] Improvements in haemangioma have also been reported in infants treated with propranolol.[4,7] Phototherapy with a pulsed dye laser has also been reported to be effective;[8] a randomised study of this method found no benefit compared with observation only,[9] but treatment is still recommended by some[10] for problematic lesions.

1. Drolet BA, *et al.* Hemangiomas in children. *N Engl J Med* 1999; **341**: 173–81.
2. Enjolras O, *et al.* Management of alarming hemangiomas in infancy: a review of 25 cases. *Pediatrics* 1990; **85**: 491–8.
3. Sadan N, Wolach B. Treatment of hemangiomas of infants with high doses of prednisone. *J Pediatr* 1996; **128**: 141–6.
4. Yap E-Y, *et al.* Periocular capillary hemangioma: a review for pediatricians and family physicians. *Mayo Clin Proc* 1998; **73**: 753–9.
5. Payarols JP, *et al.* Treatment of life-threatening infantile hemangiomas with vincristine. *N Engl J Med* 1995; **333**: 69.
6. Léauté-Labrèze C, *et al.* Propranolol for severe hemangiomas of infancy. *N Engl J Med* 2008; **358**: 2649–51.
7. Sans V, *et al.* Propranolol for severe infantile hemangiomas: follow-up report. *Pediatrics* 2009; **124**: 983. Full version: http://pediatrics.aappublications.org/cgi/reprint/124/3/e423 (accessed 09/04/10)
8. Barlow RJ, *et al.* Treatment of proliferative haemangiomas with the 585 nm pulsed dye laser. *Br J Dermatol* 1996; **34**: 700–4.
9. Batta K, *et al.* Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet* 2002; **360**: 521–7.
10. Hohenleutner U, Landthaler M. Laser treatment of childhood haemangioma: progress or not? *Lancet* 2002; **360**: 502–3.

Headache

Corticosteroids have a limited role in the management of some types of headache. Although their long-term use is not considered desirable, short courses of a corticosteroid can be effective in the prevention of cluster headache attacks during cluster periods (p. 670.1). Prednisolone may be started at an oral dose of 60 to 100 mg once daily for 2 to 5 days, then reduced by 10 mg every 2 or 3 days so that treatment is stopped after 2 to 3 weeks.[1] Prednisolone has also been given to manage the aggravation of symptoms associated with the withdrawal of analgesics in medication-

overuse headache (p. 670.2). Corticosteroids have also been used for the emergency treatment of prolonged severe attacks of migraine (status migrainosus) (p. 670.3) refractory to other drugs.

1. British Association for the Study of Headache. Guidelines for all healthcare professionals in the diagnosis and management of migraine, tension-type, cluster and medication-overuse headache. 3rd edn. (issued 18th January, 2007; 1st revision, September 2010). Available at: http://217.174.249.183/upload/NS_BASH/2010_BASH_Guidelines.pdf (accessed 21/06/11)

Herpes infections

Although corticosteroids alone are contra-indicated for most forms of ocular herpes simplex infection (p. 955.2), which should be treated with a topical antiviral, a combination of corticosteroid and antiviral may be indicated for herpes simplex stromal keratitis. For discussion of the use of corticosteroids in Bell's palsy, which may be associated with herpes simplex virus, see p. 1601.2, and for discussion of their role in postherpetic neuralgia, see p. 10.3.

Hypercalcaemia

For a description of the treatment of hypercalcaemia, including the specific role of corticosteroids, see p. 1775.3 and p. 1167.2.

Hypersensitivity vasculitis

Hypersensitivity vasculitis is usually associated with an antigenic stimulus, either exogenous (e.g. a drug[1] or microbe), or endogenous (e.g. an immune complex associated with connective tissue disease). The term covers a heterogeneous group of disorders, many of which are associated with some underlying disease process (including infections, malignant neoplasms and disorders such as rheumatoid arthritis or SLE), as well as vasculitis of less clear aetiology such as Henoch-Schönlein purpura, a disease typically seen in prepubertal males. There is a suggestion that such a broad grouping is inappropriate, and that the term 'hypersensitivity vasculitis' should not be used;[2] however, it continues to be found in the literature.

Hypersensitivity vasculitis is characterised by small vessel involvement (arterioles and venules), particularly of the skin, and skin manifestations such as purpura, rashes, and urticaria predominate. Neutrophil debris is typically present around the vessel (**leucocytoclastic vasculitis**). However other organ systems may also be involved: in **Henoch-Schönlein purpura**, the skin lesions are associated with arthralgia, abdominal pain and other gastrointestinal symptoms, and glomerulonephritis.[3] Although not always immediately apparent, renal impairment may be delayed, and progress to end-stage renal failure.[4]

The prognosis is typically much better in hypersensitivity vasculitis than in the other major vasculitic syndromes, and most cases resolve spontaneously. Where a recognised antigenic stimulus is present it should be removed if possible, e.g. by withdrawal of a drug[1] or by appropriate therapy of infection. Hypersensitivity vasculitis generally responds less well to conventional drug therapy than other vasculitic syndromes. Nonetheless, where disease persists or results in organ dysfunction, a corticosteroid should be given, typically oral prednisone or prednisolone 60 mg, or 1 mg/kg daily, tapered rapidly until therapy can be stopped. Plasmapheresis has also been used, but the use of cytotoxic immunosuppressants is less well established. However azathioprine[4] and cyclophosphamide[5] have been used successfully with corticosteroids. Anecdotal reports of excellent responses to dapsone in Henoch-Schönlein purpura exist.[6] Other drugs that have been tried include danazol,[7] pentoxifylline,[8] the latter sometimes with dapsone,[8] and normal immunoglobulin.[9]

1. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; 36: 130–47.
2. Jennette JC, *et al.* Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187–92.
3. Tizard EJ. Henoch-Schönlein purpura. *Arch Dis Child* 1999; 80: 380–3.
4. Foster BJ, *et al.* Effective therapy for severe Henoch-Schonlein purpura nephritis with prednisone and azathioprine: a clinical and histopathologic study. *J Pediatr* 2000; 136: 370–5.
5. Worm M, *et al.* Hypocomplementaemic urticarial vasculitis: successful treatment with cyclophosphamide-dexamethasone pulse therapy. *Br J Dermatol* 1998; 139: 704–7.
6. Hoffbrand BI. Dapsone in Henoch-Schönlein purpura—worth a trial. *Postgrad Med J* 1991; 67: 961–2.
7. Lee YJ, *et al.* Danazol for Henoch-Schönlein purpura. *Ann Intern Med* 1993; 118: 827.
8. Nürnberg W, *et al.* Synergistic effects of pentoxifylline and dapsone in leucocytoclastic vasculitis. *Lancet* 1994; 343: 491.
9. Rostoker G, *et al.* High-dose immunoglobulin therapy for severe IgA nephropathy and Henoch-Schönlein purpura. *Ann Intern Med* 1994; 120: 476–84.

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an immune-mediated disorder characterised by increased destruction and impaired production of platelets, resulting in low platelet counts and an increased risk of bruising and bleeding. Primary ITP has no obvious underlying cause. This condition has been commonly called idiopathic thrombocytopenic purpura, and also known as auto-immune thrombocytopenic purpura, but immune thrombocytopenia has been advocated as the preferred term because symptoms of bleeding are absent or minimal in many patients. It has also been described as having acute and chronic phases, but an alternative categorisation of newly-diagnosed, persistent (3 to 12 months after diagnosis), and chronic (lasting more than 12 months), has been proposed. A platelet count of less than 150×10^9 cells/litre has generally been used as a threshold for diagnosis. However, a lower threshold of 100×10^9 cells/litre has been suggested, to account for population variation and physiological pregnancy-related thrombocytopenia.[1] Secondary ITP may be associated with auto-immune diseases, viral infections, and exposure to certain drugs.

Treatment. Consensus documents,[2] guidelines,[3] and reviews[4,5] of the management of primary ITP have been published. The main goal of therapy is to maintain a platelet count that prevents major bleeding, rather than attempting to normalise counts. Treatment is generally considered when counts have fallen to 30 to 50×10^9 cells/litre. Corticosteroids are the mainstay of initial treatment for adults with newly-diagnosed primary ITP, usually given as oral prednisone or prednisolone 0.5 to 2 mg/kg daily for 2 to 4 weeks, then tapered. A response usually occurs within several days to weeks. High-dose parenteral methylprednisolone has also been used, and there is limited evidence of benefit from pulsed high-dose oral dexamethasone. Intravenous normal immunoglobulin may be used when corticosteroids are contra-indicated, or added to corticosteroid therapy when a more rapid response is needed. Anti-D immunoglobulin is an alternative for rhesus-positive non-splenectomised patients.

A range of treatments have been used for second-line therapy in adults who have not responded to, or have relapsed after, first-line treatment.[2,3] Splenectomy can provide sustained remission in the majority of patients, but a delay in surgery for at least 6 months should be considered because spontaneous improvement or late remission can occur 6 to 12 months after diagnosis. Vaccination against meningococcal, pneumococcal, and *Haemophilus influenzae* type b infection are recommended in patients who undergo splenectomy, because of the lifelong risks of uncontrolled infection. Opinions differ about the value of lifelong antibacterial prophylaxis (see also Spleen Disorders, p. 207.3). A range of second-line medical options may be considered, but none has a clear advantage and so choice for the individual patient depends on bleeding history, comorbidities, adverse effects of long-term therapy, and compliance. Immunosuppressive drugs that may be considered include azathioprine, ciclosporin, cyclophosphamide, mycophenolate mofetil, and vinca alkaloids (vinblastine or vincristine); response rates of at least 50% are possible but an effect may take several weeks to occur. Benefit from a 4-week course of rituximab has also been reported, but remission is not sustained in many patients and re-treatment may be needed. Dapsone has been used for its corticosteroid-sparing effect; it may delay splenectomy but splenectomised patients have a low response rate. The attenuated androgen danazol appears to be more effective in older women and splenectomised patients, but response can be slow (3 to 6 months). The thrombopoietin receptor agonists eltrombopag and romiplostim stimulate platelet production and may be used second-line; however, continuous therapy is needed and thrombocytopenia can become worse if treatment is stopped.

A rapid increase in platelet count may be needed by patients at high risk of bleeding, those with active CNS, gastrointestinal, or genito-urinary bleeding, and those needing surgery. Management may include a combination of corticosteroid (such as intravenous methylprednisolone) with normal immunoglobulin, platelet infusions, and antifibrinolytics (such as aminocaproic acid and tranexamic acid). Menstrual bleeding can be reduced by a progestogen-containing intra-uterine contraceptive device or oral contraceptive.[2]

Gestational thrombocytopenia is typical in normal *pregnancy* and may exacerbate or cause the relapse of pre-existing primary ITP. Although some experts believe that there is insufficient evidence to recommend platelet thresholds for treatment,[3] others suggest that in the first two trimesters treatment should be given when the patient is symptomatic, has a platelet count below 20 to 30×10^9 cells/litre, or when an increase in platelet count is considered necessary to be safe for procedures.[2] Evidence for recommending safe platelet counts is lacking, but some have suggested thresholds of at least 75×10^9 cells/litre for spinal or epidural anaesthesia, and at least 50×10^9 cells/litre for caesarean section.[2] Treatment of maternal ITP is similar to that used in non-pregnant women, based on corticosteroids and normal immunoglobulin or anti-D immunoglobulin.[2,3] However, other treatments such as cytotoxics, rituximab, and thrombopoietin receptor agonists are generally avoided in pregnancy. If splenectomy is necessary, it should be performed in the second trimester; it may increase the risk of pregnancy loss in the first trimester and becomes technically difficult in the third trimester.

Neonatal thrombocytopenia may occur secondary to maternal ITP and last for months.[2] Although treatment is rarely needed, neonates may be given normal immunoglobulin to manage haemorrhage or if platelet counts are below 20×10^9 cells/litre.

Serious bleeding does not occur in most *children* with primary ITP, despite very low platelet counts. At least two-thirds of young patients will improve spontaneously within 6 months of diagnosis, and remissions are generally durable. Newly-diagnosed primary ITP can therefore be managed initially by observation, regardless of platelet count, with drug therapy reserved for patients with moderate to severe bleeding, or at significant risk of bleeding. First-line therapy is similar to that recommended for adults, consisting of intravenous normal immunoglobulin or anti-D immunoglobulin, and short courses of prednisone or prednisolone. For children with persistent or chronic ITP, first-line treatments may be repeated, but in unresponsive disease options include high-dose dexamethasone, high-dose methylprednisolone, or rituximab. Experience with other treatments is more limited. Long-term corticosteroid treatment and cytotoxics should be used with extreme care because of their adverse effects in children. Splenectomy is generally deferred for as long as possible because of the high rates of spontaneous remission in children, and because the risk of death from ITP is extremely low and significantly less than that from postsplenectomy sepsis.[2,3]

Secondary ITP is generally managed by treating the underlying condition or withdrawing the offending drug.

1. Rodeghiero F, *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood* 2009; 113: 2386–93.
2. Provan D, *et al.* International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood* 2010; 115: 168–86.
3. Neunert C, *et al.* The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. *Blood* 2011; 117: 4190–4207.
4. Cuker A, Cines DB. Immune thrombocytopenia. *Hematology Am Soc Hematol Educ Program* 2010; 2010: 377–84.
5. Liebman HA, Pullarkat V. Diagnosis and management of immune thrombocytopenia in the era of thrombopoietin mimetics. *Hematology Am Soc Hematol Educ Program* 2011; 2011: 384–90.

Infections

Although long-term corticosteroid therapy has an adverse effect on the body's response to infection (see Effects on Immune Response, under Adverse Effects, p. 1617.2), the judicious use of corticosteroids, usually on a short-term basis, with appropriate anti-infective drugs, may have a beneficial effect on the symptoms of selected acute infections, and may on occasions be life-saving.

For further comment on the use of corticosteroids in ocular herpes infections, infectious mononucleosis, leishmaniasis, leprosy, meningitis, pneumocystis pneumonia in AIDS patients, septic shock, and tuberculosis, see under the relevant headings in this section.

Infectious mononucleosis

Discussions on the use of corticosteroids in infectious mononucleosis (glandular fever—see Epstein-Barr Virus Infections, p. 955.1) usually consider that although all cases would respond promptly to therapy, only patients with an unduly prolonged infection and those with an exceptionally severe sore throat that interferes with respiratory function should be treated with a corticosteroid.[1,2] Some may consider using corticosteroids in patients with aplastic anaemia, thrombocytopenia, haemolytic anaemia, encephalitis, pericarditis, or myocarditis associated with infection by the Epstein-Barr virus. The corticosteroid used, dosage, route, and duration of treatment is variable. Dexamethasone, methylprednisolone, and prednisolone have all been tried in infectious mononucleosis. While corticosteroid treatment is considered relatively safe in infectious mononucleosis, impaired immunity might theoretically increase the risk of Epstein-Barr virus-related tumours in later life.

1. Tynell E, *et al.* Acyclovir and prednisolone treatment of acute infectious mononucleosis: a multicenter, double-blind, placebo-controlled study. *J Infect Dis* 1996; 174: 324–31.
2. Thompson SK, *et al.* Infectious mononucleosis and corticosteroids: management practices and outcomes. *Arch Otolaryngol Head Neck Surg* 2005; 131: 900–4.

Inflammatory bowel disease

Corticosteroids with aminosalicylates form the mainstay of treatment for active ulcerative colitis and Crohn's disease (see Inflammatory Bowel Disease, p. 1808.3). In moderate to severe acute disease systemic corticosteroids are indicated for initial management, either orally or in the most severe cases intravenously. Doses are high initially and are gradually reduced as symptoms resolve. In patients with

disease confined to the distal colon or rectum, local topical therapy with suppositories, rectal foams, or enemas of corticosteroids may be appropriate. Oral or rectal formulations of poorly absorbed or rapidly metabolised corticosteroids such as beclometasone, budesonide, or tixocortol have been developed in the hope of producing local improvement without systemic effects.

Interstitial lung disease

Interstitial lung disease (diffuse parenchymal lung disease) represents a large and heterogeneous group of inflammatory disorders that have in common a thickening of the interstitial walls between alveoli. In some cases, particularly in the early stages, this is due to accumulation of inflammatory cells in the interstitium, and control of inflammation can reverse the changes; however, when fibrotic changes to the alveolar walls take place these are usually irreversible. The causes of chronic interstitial lung disease are numerous and include pneumoconioses due to inhalation of inorganic dusts (as in asbestosis and silicosis); extrinsic allergic alveolitis due to inhalation of, usually, organic antigens (as in farmers' lung, bird fanciers' lung, and many similar occupational disorders); idiopathic pulmonary fibrosis (cryptogenic fibrosing alveolitis); adverse effects of drugs such as bleomycin; sarcoidosis; lung disease associated with collagen vascular disorders such as rheumatoid arthritis and SLE, or with the vasculitides; histiocytic syndromes; and pulmonary eosinophilic syndromes. Idiopathic pulmonary fibrosis (below) and sarcoidosis (p. 1612.2) are probably the most common chronic interstitial lung diseases.[1]

The symptoms of interstitial lung disease are usually insidious and non-specific, and may include dyspnoea of varying severity, usually first noticed on exertion, cough, and fatigue; fine crackling sounds (rales) on breathing and finger clubbing occur in some forms. If the disease progresses, respiratory failure becomes more severe, and eventually may prove fatal.

Where a causative agent can be identified, initial treatment is to prevent exposure but where inflammation persists, or where the causation is uncertain, corticosteroids are the mainstay of treatment (despite a lack of controlled studies for efficacy),[1] in an attempt to control inflammation and preserve as much normal tissue as possible. The management of idiopathic pulmonary fibrosis is discussed in more detail below.

Idiopathic pulmonary fibrosis is one of the idiopathic interstitial pneumonias, a subgroup of interstitial lung disease. The terminology used for the idiopathic interstitial pneumonias has been confusing, but improved diagnostic methods have facilitated the development of an internationally accepted classification system.[2] The terms idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis are now synonymous, and are used for a distinctive type of chronic fibrosing interstitial pneumonia of unknown cause. It is associated with a specific histologic pattern known as usual interstitial pneumonia, in which there is interstitial inflammation, fibrosis, and honeycomb changes. The clinical course is generally of gradual deterioration, occasionally with periods of rapid decline, and a median length of survival after diagnosis of between 2.5 and 3.5 years. Idiopathic pulmonary fibrosis should be distinguished from the other forms of idiopathic interstitial pneumonia, which may differ in prognosis and response to corticosteroid therapy; these are non-specific interstitial pneumonia, cryptogenic organising pneumonia (bronchiolitis obliterans organising pneumonia), acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia, and lymphoid interstitial pneumonitis.

Guidelines and reviews state that pharmacologic therapy for idiopathic pulmonary fibrosis has no definitive, proven benefit.[1,3,4] Corticosteroids have traditionally been used, based on observational reports of a symptomatic response to treatment in about 50% of patients, and an improvement in lung function in up to 25%. However, these early reports were likely to have included a heterogeneous mix of patients that included other types of idiopathic interstitial pneumonias.[1,3] Although randomised placebo-controlled studies have not been done, several retrospective studies found no evidence of benefit from high-dose corticosteroids, and they are not recommended as monotherapy in patients with definite idiopathic pulmonary fibrosis.[1,3] The use of a corticosteroid with an immunosuppressive or cytotoxic drug, particularly azathioprine or cyclophosphamide, has also been tried but these dual-therapy combinations are not recommended.[1,3] However, there was some evidence from a randomised study that the addition of acetylcysteine to prednisone and azathioprine slowed the rate of decline in lung function.[6] Triple oral therapy has been recommended by the British Thoracic Society, consisting of prednisolone (500 micrograms/kg daily, tapering over 3 months to 125 micrograms/kg daily) with azathioprine (2 to 3 mg/kg daily, to a maximum of 150 mg daily) and acetylcysteine (600 mg three times daily).[1] However, further study is required to confirm the benefits of this combination. Joint guidelines (from America, Europe, Japan and Latin America)[3] have also suggested that this combination, as well as acetylcysteine monotherapy, may be of use in a minority of patients. There is limited evidence to suggest that the antifibrotic pirfenidone may improve pulmonary function and progression-free survival,[7] and it too has been proposed as a reasonable choice in a minority of patients.[3]

Microvascular thrombosis may be an important pathogenic process in idiopathic pulmonary fibrosis,[1] and anticoagulation might have a beneficial effect on survival but further studies are needed.[1,3]

Many other drugs have been tried in patients with idiopathic pulmonary fibrosis.[1,3,4,7] Ciclosporin has been used adjunctively and also as a corticosteroid-sparing treatment, but data are too limited to support its use.[3,4] Colchicine has been suggested to be as effective as corticosteroids, however, studies have generally shown no evidence of survival benefit, and it is not recommended.[3,4] There are reports of response to penicillamine, but controlled studies are lacking, and in view of its adverse effects, its use is generally not recommended.[4] Despite promising preliminary results, a large controlled study of interferon gamma found no significant effects on mortality compared with placebo.[8] Experimental strategies include the use of relaxin, suramin, sildenafil, endothelin receptor antagonists, angiotensin II receptor antagonists, and gene therapy.[3,4]

In patients in whom other options fail, lung transplantation (p. 1937.3) should be considered.[1,3]

1. Wells AU, *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; 63 (suppl V): v1–v58. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/DPLD/Guidelines/Thorax%20Sept%2008.pdf (accessed 21/04/10)
2. American Thoracic Society. European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277–304. Also available at: http://ajrccm.atsjournals.org/cgi/reprint/165/2/277.pdf (accessed 21/06/10)
3. Raghu G, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824. Also available at: http://www.thoracic.org/statements/resources/respiratory-disease-adults/Ipf0311.pdf (accessed 26/08/11)
4. Selman M, *et al.* Idiopathic pulmonary fibrosis: pathogenesis and therapeutic approaches. *Drugs* 2004; 64: 405–30.
5. Richeldi L, *et al.* Corticosteroids for idiopathic pulmonary fibrosis. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2003 (accessed 18/07/05).
6. Demedts M, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; 353: 2229–42.
7. Spagnolo P, *et al.* Non-steroid agents for idiopathic pulmonary fibrosis. Available in The Cochrane Database of Systematic Reviews: Issue 9. Chichester: John Wiley; 2010 (accessed 19/09/11).
8. King TE, *et al.* Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009; 374: 222–8.

Leishmaniasis

Corticosteroids may be required to control severe inflammation in patients with mucocutaneous leishmaniasis (p. 923.1), although pentavalent antimony is usually the drug used for initial treatment.

Leprosy

Type 1 lepra (reversal) reactions in patients with leprosy (p. 188.3) frequently respond to high-dose corticosteroids (for example 40 to 60 mg of prednisolone daily) started immediately and given for several days.[1] Doses may be reduced over several weeks or months. Corticosteroids may also be used for type II reactions.

It has been considered that corticosteroid treatment of nerve function impairment should be started within 6 months of onset, as the earlier that treatment was started, the more likely it was that function would be restored. A standardised regimen in which the usual adult dose was 40 mg daily of prednisolone for 4 weeks, tapered over the next 12 weeks, has been reported to be successful in the field management of acute nerve function impairment,[2] as has a regimen consisting of 30 mg of prednisone for 2 weeks tapered down with a minimum duration of 10 weeks.[3] However, a subsequent study[4] in patients with mild nerve impairment for less than 6 months, and another in patients with established sensory impairment[5] both failed to show any benefit from a tapered corticosteroid regimen. There was evidence that sensory impairment may undergo some degree of spontaneous recovery, which casts doubt on previous reports of benefit from uncontrolled studies of corticosteroids. The use of a lower dose prophylactic regimen has also been studied, starting with prednisolone 20 mg daily for 3 months then tapering in the fourth month.[6] Although the incidence of new leprosy-related reactions and associated nerve function impairment in all patients was reduced during corticosteroid treatment, there appeared to be a rebound after this was stopped and the initial beneficial effect was not sustained at 1 year. Interestingly, however, subgroup analysis suggested that existing nerve function impairment at diagnosis may affect the outcome; after 4 months of prophylaxis, a significant reduction in acute reactions or new nerve function impairment was seen only in those without initial evidence of impairment although, as before, this was not sustained.

1. WHO. WHO expert committee on leprosy. *WHO Tech Rep Ser 874* 1998. Available at: http://libdoc.who.int/trs/WHO_TRS_874.pdf (accessed 26/08/08)
2. Croft RP, *et al.* Field treatment of acute nerve function impairment in leprosy using a standardized corticosteroid regimen—first year's experience with 100 patients. *Lepr Rev* 1997; 68: 316–25.
3. Bernink EHM, Voskens JEJ. Study on the detection of leprosy reactions and the effect of prednisone on various nerves, Indonesia. *Lepr Rev* 1997; 68: 225–32.
4. van Brakel WH, *et al.* The prognostic importance of detecting mild sensory impairment in leprosy: a randomized controlled trial (TRIPOD 2). *Lepr Rev* 2003; 74: 300–10.
5. Richardus JH, *et al.* Treatment with corticosteroids of long-standing nerve function impairment in leprosy: a randomized controlled trial (TRIPOD 3). *Lepr Rev* 2003; 74: 311–18.
6. Smith WCS, *et al.* Steroid prophylaxis for prevention of nerve function impairment in leprosy: randomised placebo controlled trial (TRIPOD 1). Abridged version: *BMJ* 2004; 328: 1459–62. Full version: http://www.bmj.com/cgi/reprint/328/7454/1459 (accessed 09/11/07)

Lichen

Lichen planus (p. 1685.2) is generally controlled with corticosteroids applied topically or, occasionally, injected intralesionally; systemic corticosteroids (usually prednisone or prednisolone) are used for severe erosive lichen planus, generalised cutaneous disease, and acute exacerbations.[1,2] Prednisone has generally been used in oral doses of 30 to 60 mg daily, for courses of 4 to 6 weeks.[1] Shorter courses may be of value: prednisolone (30 mg daily for 10 days) was reported to be effective and safe for mild or moderately severe lichen planus.[3]

Topically applied corticosteroids form the mainstay of treatment of lichen sclerosus (p. 1685.2). UK guidelines recommend clobetasol propionate 0.05% ointment, usually applied once daily at night for 4 weeks, then on alternate nights for 4 weeks, then twice weekly for 4 weeks, after which the patient should be reviewed. Once the condition is under control, the frequency of application may be increased as necessary when symptoms recur.[4] Another review has suggested that after inducing remission with a potent topical corticosteroid, hydrocortisone 1% may be applied once daily for long-term control of the condition in children.[5]

1. Cribier B, *et al.* Treatment of lichen planus: an evidence-based medicine analysis of efficacy. *Arch Dermatol* 1998; 134: 1521–30.
2. Agarwal R, Saraswat A. Oral lichen planus: an update. *Drugs Today* 2002; 38: 533–47.
3. Kellett JK, Rad RD. Treatment of lichen planus with a short course of oral prednisolone. *Br J Dermatol* 1990; 123: 550–1.
4. Neill SM, *et al.* British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol* 2010; 163: 672–82. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Lichen%20Sclerosus%20Guidelines%202010.pdf (accessed 31/01/11)
5. Smith SD, Fischer G. Paediatric vulval lichen sclerosus. *Australas J Dermatol* 2009; 50: 243–8.

Liver disorders

Corticosteroids are considered to be useful in chronic active hepatitis (p. 1602.3). There is some disagreement over the benefit from corticosteroid therapy in alcoholic liver disease with hepatic encephalopathy,[1–4] and they do not appear to be of benefit in acute hepatic failure.[5] Corticosteroid therapy may however be of benefit in sclerosing cholangitis.[6]

No treatment has proven unequivocally successful in the management of primary biliary cirrhosis (p. 2638.3). Corticosteroids are one of a number of drugs for which reports of benefit exist, but their use has been restricted as they may exacerbate bone disease.

1. Imperiale TF, McCullough AJ. Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials. *Ann Intern Med* 1990; 113: 299–307.
2. Ramond M-J, *et al.* A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *N Engl J Med* 1992; 326: 507–12.
3. Wrona SA, Tankanow RM. Corticosteroids in the management of alcoholic hepatitis. *Am J Hosp Pharm* 1994; 51: 347–53.
4. Christensen E, Gluud C. Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables. *Gut* 1995; 37: 113–18.
5. Caraceni P, Van Thiel DH. Acute liver failure. *Lancet* 1995; 345: 163–9.
6. Lindor KD, *et al.* Advances in primary sclerosing cholangitis. *Am J Med* 1990; 89: 73–80.

Male infertility

Immunosuppressive treatment with corticosteroids has been given for male infertility (p. 2253.1) due to low-grade auto-immune orchitis.[1] Corticosteroids have also been used in men with autoantibodies to spermatozoa. Various regimens have been tried, such as giving the man a corticosteroid for a set number of days during the partner's menstrual cycle, or giving a continuous low-dose for several months.[2] However, there is a lack of evidence of benefit from substantial controlled studies and the use of corticosteroids is not generally recommended. They might,

however, be considered for men with autoantibodies who have failed assisted reproductive techniques.[1]

1. Haidl G. Management strategies for male factor infertility. *Drugs* 2002; 62: 1741–53.
2. Lombardo F, *et al.* Antisperm immunity in natural and assisted reproduction. *Hum Reprod Update* 2001; 7: 450–6.

Malignant neoplasms

Corticosteroids are extensively prescribed in malignant disease for the relief of pain, nerve compression, or raised intracranial pressure; to alleviate dyspnoea, effusion, or hypercalcaemia; to counteract adverse effects of other therapies such as antineoplastic-induced nausea and vomiting or radiation-induced inflammation; and in the management of cachexia and to improve mood and sense of well-being.[1] In addition they form an important part of multidrug anticancer regimens used for various haematological malignancies such as acute lymphoblastic leukaemia (p. 692.3) and Hodgkin's disease (p. 696.1). In contrast, it has been postulated that the use of corticosteroids in patients with solid, non-haematological tumours might induce resistance in cancer cells to cytotoxic therapy, and increase the risk of treatment failure, although clinical evidence for this is lacking.[2]

1. Twycross R. The risks and benefits of corticosteroids in advanced cancer. *Drug Safety* 1994; 11: 163–78.
2. Rutz HP. Effects of corticosteroid use on treatment of solid tumours. *Lancet* 2002; 360: 1969–70.

Meningitis

Corticosteroids may be given as adjuncts to antibacterial therapy in bacterial meningitis (p. 191.1), in the hope of moderating any neurological sequelae; there is some evidence that dexamethasone, especially if given early, may reduce the risk of deafness in children and reduce mortality in adults.

Mouth ulceration

Local treatment of mouth ulcers (p. 1811.2) often involves a topical corticosteroid for symptomatic relief. Systemic corticosteroids have occasionally been given where there is severe underlying disease.

Multiple sclerosis

Corticosteroids are often used in the management of multiple sclerosis (p. 996.3). Corticosteroid therapy reduces the duration of the relapse and accelerates recovery, but it is unknown whether it alters the course of the disease in the long term.[1,2] Methylprednisolone has superseded corticotropin and prednisolone as the drug of choice. Methylprednisolone is usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days, sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g of methylprednisolone daily have been tried.[3] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis[4] although the effect was not sustained beyond 2 years.[5] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[6] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[7]

In patients with primary progressive disease, the benefits of short-course methylprednisolone lasted no longer than 3 months[8] although, in patients with secondary progressive disease, a preliminary study has suggested that progression may be delayed by intermittent high-dose methylprednisolone therapy.[9]

1. Rudick RA, *et al.* Management of multiple sclerosis. *N Engl Med J* 1997; 337: 1604–11.
2. Filippini G, *et al.* Corticosteroids or ACTH for acute exacerbations in multiple sclerosis. Available in The Cochrane Database of Systematic Reviews; Issue 4, Chichester: John Wiley; 2000 (accessed 12/05/05).
3. Oliveri RL, *et al.* Randomized trial comparing two different high doses of methylprednisolone in MS: a clinical and MRI study. *Neurology* 1998; 50: 1833–6.
4. Beck RW, *et al.* The effect of corticosteroids for acute optic neuritis on the subsequent development of multiple sclerosis. *N Engl J Med* 1993; 329: 1764–9.
5. Beck RW, *et al.* The optic neuritis treatment trial: three-year follow-up results. *Arch Ophthalmol* 1995; 113: 136–7.
6. Sellebjerg F, *et al.* Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS. *Neurology* 1998; 51: 529–34.
7. Barnes D, *et al.* Randomised trial of oral and intravenous methylprednisolone in acute relapses of multiple sclerosis. *Lancet* 1997; 349: 902–6.
8. Cazzato G, *et al.* Double-blind, placebo-controlled, randomized, crossover trial of high-dose methylprednisolone in patients with chronic progressive form of multiple sclerosis. *Eur Neurol* 1995; 35: 193–8.
9. Goodkin DE, *et al.* A phase II study of IV methylprednisolone in secondary-progressive multiple sclerosis. *Neurology* 1998; 51: 239–45.

Muscular dystrophies

Muscular dystrophies are a range of inherited myopathies in which there is progressive degeneration of muscle fibres and associated muscle weakness. They may be classified according to the mode of inheritance. The most common type is the fatal recessive X-linked **Duchenne muscular dystrophy** (DMD) in which there is a deficiency in the structural muscle protein dystrophin. There is no effective therapy that affects the ultimate outcome of the various muscular dystrophies. Management is mainly through the use of physiotherapy, supports, and surgery. Drug treatment has been tried for symptomatic management, but generally the number of patients studied has been small. However, corticosteroids have been shown to be effective in increasing muscle strength and function in children for 6 months to 2 years;[1] prednisone or prednisolone 750 micrograms/kg daily is considered to be the most effective dose,[1-3] with gradual tapering to doses as low as 300 micrograms/kg daily if necessary.[2] Improvement does not appear to be sustained to the same degree with alternate-day therapy;[4] some benefit in terms of motor function preservation has been reported with intermittent prednisone (750 micrograms/kg daily for 10 days of each month).[5] Benefit has also been seen with deflazacort[1-3,6] in doses of 900 micrograms/kg daily. It has been suggested that the failure of azathioprine to produce any beneficial effect when used alone or added to prednisone treatment might indicate that prednisone's efficacy is not due to immunosuppression.[7] There have also been reports of benefit in small numbers of patients given ciclosporin or oxandrolone; evidence to support the use of most other drugs is either conflicting or unconvincing. A small study found that supplementation with creatine monohydrate (100 mg/kg daily) significantly increased handgrip strength in the dominant hand compared with placebo; results were independent of corticosteroid use.[8] Future prospects for treatment include gene therapy, haematopoietic stem-cell therapy, or upregulation of the protein utrophin (related to dystrophin) to try to ameliorate the dystrophy.[9,10]

1. Manzur AY, *et al.* Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 22/08/08).
2. Moxley RT, *et al.* Practice parameter: corticosteroid treatment of Duchenne dystrophy. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology* 2005; 64: 13–20. Also available at: http://www.aan.com/professionals/practice/guidelines/pda/Duchenne_Muscular_Dystrophy.pdf (accessed 26/08/08)
3. Bushby K, *et al.* Report on the 124th ENMC International Workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids: 2-4 April 2004, Naarden, The Netherlands. *Neuromuscul Disord* 2004; 14: 526–34.
4. Penichel GM, *et al.* A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. *Arch Neurol* 1991; 48: 575–9.
5. Beenakker EA, *et al.* Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomized controlled trial. *Arch Neurol* 2005; 62: 128–32.
6. Bigger WD, *et al.* Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr* 2001; 138: 45–50.
7. Griggs RC, *et al.* Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). *Neurology* 1993; 43: 520–7.
8. Tarnopolsky MA, *et al.* Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. *Neurology* 2004; 62: 1771–7.
9. Emery AEH. The muscular dystrophies. *Lancet* 2002; 359: 687–95.
10. Bogdanovich S, *et al.* Therapeutics for Duchenne muscular dystrophy: current approaches and future directions. *J Mol Med* 2004; 82: 102–15.

Myasthenia gravis

Corticosteroids are the main immunosuppressants used in the management of myasthenia gravis (p. 684.1).

Nasal polyps

Nasal polyps[1-3] are outgrowths of the nasal mucosa, typically pale, smooth, translucent, and round or pear-shaped. They are often associated with a history of rhinitis or asthma; the triad of nasal polyps, asthma, and hypersensitivity to aspirin may occur. Patients typically present with obstruction, loss of smell, and often rhinorrhoea and postnasal drip.

Corticosteroids are extremely effective in reducing polyp size, either by the intranasal[4,5] or systemic route.[5,6] In the former case beginning with betamethasone sodium phosphate nasal drops, and then maintaining the reduction with an intranasal spray such as beclometasone, budesonide, or fluticasone, has been suggested.[1] Alternatively prednisone, prednisolone, or dexamethasone can be given orally; suggested regimens have included prednisone 60 mg daily, tapered over 10 or 14 days and followed by intranasal corticosteroids,[2] or dexamethasone 12, 8, and 4 mg daily, each for 3 days.[1] Surgery may be necessary where there is marked obstruction, and most patients require it at some point,[1] although polyps usually recur. Pre-operative use of systemic corticosteroids may help reduce recurrence.[2] Continued use of topical corticosteroids may reduce the frequency of relapses.[4] Antibacterials may be indicated for superimposed bacterial infection. Antihistamines, although not extensively studied, have been reported to be of benefit in nasal obstruction. Leukotriene antagonists have shown promising results, although large-scale studies are lacking; they may be indicated in patients with aspirin hypersensitivity.[5]

1. Lund VJ. Diagnosis and treatment of nasal polyps. *BMJ* 1995; 311: 141–14.
2. Slavin RG. Nasal polyps and sinusitis. *JAMA* 1997; 278: 1849–54.
3. Drake-Lee AB. Nasal polyps. *Hosp Med* 2004; 65: 264–7.
4. Badia L, Lund V. Topical corticosteroids in nasal polyposis. *Drugs* 2001; 61: 573–8.
5. Bachert C, *et al.* Pharmacological management of nasal polyposis. *Drugs* 2003; 63: 1537–52.
6. Hissaria P, *et al.* Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures. *J Allergy Clin Immunol* 2006; 118: 128–33.

Nausea and vomiting

Corticosteroids, usually in the form of dexamethasone, play an important role in antiemetic regimens (see p. 1811.3) used to combat the effects of moderately to severely emetogenic cancer chemotherapy: they have been shown to enhance the effects of both metoclopramide- and 5-HT$_3$ antagonist-based regimens. Dexamethasone is a well-established treatment for delayed emesis. It is also used in palliative care and in the prophylaxis of postoperative nausea and vomiting. A study of corticosteroid treatment in refractory hyperemesis gravidarum showed improvement in appetite, weight gain, and well-being, and suggested that corticosteroids might improve nausea and vomiting but was too small to provide conclusive evidence.[1]

1. Nelson-Piercy C, *et al.* Randomised, double-blind, placebo-controlled trial of corticosteroids for the treatment of hyperemesis gravidarum. *Br Obstet Gynaecol* 2001; 108: 9–15.

Neonatal intraventricular haemorrhage

For the suggestion that antenatal corticosteroids may reduce the incidence of intraventricular haemorrhage in neonates see p. 1128.3.

Neonatal respiratory distress syndrome

Neonatal respiratory distress syndrome is a condition of increasing respiratory distress occurring at, or shortly after, birth. It is marked by cyanosis, tachypnoea, expiratory grunting and sternal retraction. Symptoms increase in severity with progressive collapse of the lung (atelectasis), leakage of plasma into alveolar spaces, and the formation of hyaline membranes, until death occurs or slow recovery takes place from about the 2nd to 4th day. The syndrome affects mainly premature infants and its incidence increases with the degree of prematurity; severe problems are most likely in those delivered before 30 weeks of gestation. Symptoms are thought to be at least partly due to inadequate amounts of surfactant in the premature lung resulting in high internal surface tension and increased risk of alveolar collapse, but in very immature infants other factors, possibly including impaired sodium and fluid absorption from the lung, may play a role.[1]

Treatment. The optimum treatment is prevention, and previous[2] and more recent[3] UK guidelines recommend betamethasone 12 mg daily by intramuscular injection for 2 days in women in whom delivery before 34 weeks of gestation is likely. Similar recommendations apply elsewhere. In the USA, for example, antenatal corticosteroid treatment (with betamethasone or dexamethasone) is recommended for women between 24 and 34 weeks of pregnancy who show signs of premature delivery.[4] Results from a large study suggest that babies born after 37 weeks by elective caesarean section also benefit from antenatal betamethasone.[5] Betamethasone may be preferable to dexamethasone, as the latter appears to have a deleterious effect on neurodevelopment.[6] Long-term follow-up of those exposed antenatally to betamethasone showed no deleterious effects on psychological functioning[7] or on cardiovascular risk factors;[8] however, small increases in insulin resistance, albeit clinically insignificant, were noted in those exposed to the glucocorticoid. An overview of studies of antenatal corticosteroid therapy suggests that it may reduce the risk of respiratory distress syndrome by about 50% overall;[9] the risk of death, and of periventricular haemorrhage and necrotising enterocolitis is also reduced. Whether repeat courses should be considered is uncertain, although the practice has become widespread. A systematic review[10] indicated that repeat doses did reduce the occurrence and severity of neonatal lung disease and risk of serious health problems in the first few weeks of life. However, these benefits were associated with a reduction in some measures of weight and head circumference at birth and there was insufficient evidence on the long-term benefits and risks. Some have recommended that repeat doses be restricted to patients in clinical studies.[6,11] Delaying delivery with a tocolytic (see Premature Labour, p. 2131.1) may be considered to increase the time available for management with antenatal corticosteroids.[2,3] Reported benefit from adding protirelin to antenatal corticosteroids has not been borne out by 2 large multicentre studies.[12-14] The earlier of these studies actually found neonatal outcome

and maternal morbidity to be worse in those who also received protirelin.[12,13] but this conclusion has been questioned.[15,16]

In infants born with the syndrome rapid supportive care is required, which may include correction of metabolic acidosis, circulatory support, oxygen supplementation, and assisted ventilation, although there has been a lack of consensus about the most appropriate method for these.[2] Ventilation using a helium-oxygen mixture may give better results than a nitrogen-oxygen mix.[17] Another alternative is the use of partial liquid ventilation with the fluorocarbon compound perflubron.[18] Meta-analysis suggests that inhaled nitric oxide improves outcomes in infants born at or near term who are hypoxaemic,[19] but evidence of benefit in preterm infants has not been shown.[20] The majority of infants survive the acute episode with careful management, although associated complications may subsequently develop, including bronchopulmonary dysplasia (p. 1602.1), retinopathy of prematurity (p. 2120.3), and cerebral palsy. There is evidence that supplementation with inositol can significantly reduce the incidence of adverse outcomes in preterm infants.[21]

Since deficiency of surfactant is considered to play an important role in the neonatal respiratory distress syndrome, the use of surfactant replacement therapy has been intensively investigated, and is now accepted as reducing the risk of death from the disease and the development of pneumothorax and other lung complications.[2,22,23] Both natural and synthetic surfactants have been used and although both are effective results have tended to be better with the preparations of natural origin.[24-26] Natural surfactants of differing origins may also vary in their properties: poractant,[27] or calfactant,[28] have both been reported to give better responses than beractant. Surfactant is given as a suspension by endotracheal tube directly into the infant's lung, although other devices, such as nebulisers, have been investigated. Most surfactants are given in recommended doses of 100 to 200 mg/kg phospholipids. Repeat doses may be given if necessary, and a meta-analysis[29] of data from two randomised controlled studies using preparations of natural surfactant extract in neonates with established disease found a more favourable clinical outcome, including a decreased risk of pneumothorax, with multiple rather than single doses. However, in clinical practice the number of doses and the dosage interval varies. One large study[30] found that a dose of 100 mg/kg, repeated twice, was as effective as 200 mg/kg followed by up to four further doses of 100 mg/kg. Another found that 3 doses, given at 12-hour intervals with the first dose shortly after birth were more effective than the first dose alone in improving physiological findings and mortality rates in low birth-weight infants.[31] One large multicentre randomised controlled study[32] investigated the difference between giving repeat doses of a surfactant (calfactant) at a low threshold of respiratory support, as recommended by the manufacturer, versus a higher threshold. The conclusion was that efficacy was not compromised by delaying surfactant re-treatment in infants with uncomplicated respiratory distress syndrome until they had reached a higher level of respiratory support than is currently recommended, but infants with complications should continue to be treated by the currently recommended low-threshold strategy.

There has been debate whether 'prophylactic' early therapy, given immediately after birth to all infants deemed at risk of the syndrome, or delayed therapy given 2 or more hours after birth to intubated infants who have developed symptoms, is the more appropriate,[33] but the large OSIRIS study,[34] and later systematic reviews,[35-37] found in favour of early intervention, and this strategy is recommended in the UK guidelines.[2,3] However, two subsequent studies undertaken when maternal antenatal corticosteroid prophylaxis and nasal continuous positive airway pressure (CPAP) had become routine found that early stabilisation on CPAP, with surfactant only given to infants needing intubation, was associated with a reduced risk of chronic lung disease or death when compared with prophylactic surfactant.[38]

1. Barker PM, *et al.* Decreased sodium ion absorption across nasal epithelium of very premature infants with respiratory distress syndrome. *J Pediatr* 1997; 130: 373–7.
2. Report of the second working group of the British Association of Perinatal Medicine. Guidelines for good practice in the management of neonatal respiratory distress syndrome. Guideline produced in November 1998, not valid beyond 2002. Available at: http://www.bapm.org/documents/publications/rds.pdf (accessed 13/09/04)
3. Royal College of Obstetricians and Gynaecologists. Antenatal corticosteroids to prevent respiratory distress syndrome (revised February 2004). Available at: http://www.rcog.org.uk/files/rcog-corp/GT7AntenatalCorticosterodsamended.pdf (accessed 23/04/10)
4. NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. *JAMA* 1995; 273: 413–18.
5. Stutchfield P, *et al.* Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial. *BMJ* 2005; 331: 662–4.
6. Lawson EE. Antenatal corticosteroids—too much of a good thing? *JAMA* 2001; 286: 1628–30.
7. Dalziel SR, *et al.* Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ* 2005; 331: 665–8.
8. Dalziel SR, *et al.* Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005; 365: 1856–62.
9. Crowley PA. Antenatal corticosteroid therapy: a meta-analysis of the randomized trials, 1972 to 1994. *Am J Obstet Gynecol* 1995; 173: 322–35.
10. Crowther CA, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/08).
11. National Institutes of Health. Consensus development conference statement. August 17-18, 2000—antenatal corticosteroids revisited: repeat courses. *NIH Consens Statement* 2000; 17: 1–18. Available at: http://consensus.nih.gov/2000/2000AntenatalCorticosteroidsRevisited12html.htm (accessed 06/07/06)
12. ACTOBAT Study Group. Australian collaborative trial of antenatal thyrotropin-releasing hormone (ACTOBAT) for prevention of neonatal respiratory disease. *Lancet* 1995; 345: 877–82.
13. Crowther CA, *et al.* Australian Collaborative Trial of antenatal thyrotropin-releasing hormone: adverse effects at 12-month follow-up. *Pediatrics* 1997; 99: 311–17.
14. Ballard RA, *et al.* Antenatal thyrotropin-releasing hormone to prevent lung disease in preterm infants. *N Engl J Med* 1998; 338: 493–8.
15. Moya FR, Maturana A. Thyrotropin-releasing hormone for prevention of neonatal respiration disease. *Lancet* 1995; 345: 1572–3.
16. McCormick MC. The credibility of the ACTOBAT follow-up study. *Pediatrics* 1997; 99: 476–8.
17. Elleau C, *et al.* Helium-oxygen mixture in respiratory distress syndrome: a double-blind study. *J Pediatr* 1993; 122: 132–6.
18. Leach CL, *et al.* Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 1996; 335: 761–7.
19. Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 22/08/08).
20. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 22/08/08).
21. Howlett A, Ohlsson A. Inositol for respiratory distress syndrome in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/05/05).
22. Schwartz RM, *et al.* Effect of surfactant on morbidity, mortality, and resource use in newborn infants weighing 500 to 1500 g. *N Engl J Med* 1994; 330: 1476–80.
23. Walti H, Monset-Couchard M. A risk-benefit assessment of natural and synthetic exogenous surfactants in the management of neonatal respiratory distress syndrome. *Drug Safety* 1998; 18: 321–37.
24. Halliday HL. Natural vs synthetic surfactants in neonatal respiratory distress syndrome. *Drugs* 1996; 51: 226–37.
25. Hudak ML, *et al.* A multicenter randomized, masked comparison trial of natural versus synthetic surfactant for the treatment of respiratory distress syndrome. *J Pediatr* 1996; 128: 396–406.
26. Soll RF, Blanco F. Natural surfactant extract versus synthetic surfactant for neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 12/05/05).
27. Speer CP, *et al.* Randomised clinical trial of two treatment regimens of natural surfactant preparations in neonatal respiratory distress syndrome. *Arch Dis Child* 1995; 72: F8–F13.
28. Bloom BT, *et al.* Randomized double-blind multicenter trial of Survanta (SURV) and Infasurf (IS). *Pediatr Res* 1994; 35: 326.
29. Soll R, Özek E. Multiple versus single doses of exogenous surfactant for the prevention or treatment of neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 23/04/10).
30. Halliday HL, *et al.* Multicentre randomised trial comparing high and low dose surfactant regimens for the treatment of respiratory distress syndrome (the Curosurf 4 trial). *Arch Dis Child* 1993; 69: 276–80.
31. Corbet A, *et al.* Double-blind, randomized trial of one versus three prophylactic doses of synthetic surfactant in 826 neonates weighing 700 to 1100 grams: effects on mortality rate. *J Pediatr* 1995; 126: 969–78.
32. Kattwinkel J, *et al.* High- versus low-threshold surfactant retreatment for neonatal respiratory distress syndrome. *Pediatrics* 2000; 106: 282–8.
33. Dunn MS. Surfactant replacement therapy: prophylaxis or treatment? *Pediatrics* 1993; 92: 148–50.
34. The OSIRIS Collaborative Group (Open Study of Infants at high risk of or with Respiratory Insufficiency—the role of surfactant). Early versus delayed neonatal administration of a synthetic surfactant—the judgement of OSIRIS. *Lancet* 1992; 340: 1363–9.
35. Morley CJ. Systematic review of prophylactic vs rescue surfactant. *Arch Dis Child* 1997; 77: F70–4.
36. Bahadue FL, Soll R. Early versus delayed selective surfactant treatment for neonatal respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews: Issue 11. Chichester: John Wiley; 2012 (accessed 09/01/13).
37. Stevens TP, *et al.* Early surfactant administration with brief ventilation vs. selective surfactant and continued mechanical ventilation for preterm infants with or at risk for respiratory distress syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 09/01/13).
38. Rojas-Reyes MX, *et al.* Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2012 (accessed 09/01/13).

Optic neuropathies

Causes of optic neuropathies are diverse, and they may be classified by their aetiology.[1,2] Ischaemic optic neuropathies, of which the acute anterior form is most common, may be caused by vasculitic syndromes (p. 1615.2) such as giant cell arteritis (p. 1604.2).[3] Inflammatory optic neuropathies (optic neuritis) may be caused by infectious disease, immune-mediated disorders such as Behçet's disease (p. 1601.1), sarcoidosis (p. 1612.2), or demyelination of the optic nerve such as occurs with multiple sclerosis (p. 996.3).[4,5] Other causes include hereditary disorders, trauma, or compression. Vitamin or nutritional deficiency (often due to alcohol abuse) or toxicity (due to drugs such as amiodarone, digoxin, or isoniazid) may also lead to optic neuropathy.[1,2] Clinical features such as pattern of visual field loss and pain can aid diagnosis.[2]

Management will depend on the type of neuropathy and any underlying disease. Individual studies have reported benefit with corticosteroids. Improvement in vision was reported in patients with auto-immune optic neuropathy after 5 to 7 days of treatment with high doses of intravenous methylprednisolone (1 to 2 g daily) or oral prednisolone (80 to 400 mg daily).[6] In some patients, recurrent visual loss required repeated high-dose intravenous methylprednisolone, an increase in oral prednisolone dosage, or additional immunosuppressants, but in many patients visual benefits were maintained even when treatment was withdrawn. Visual recovery has also been reported in patients with optic neuritis of unknown aetiology given intravenous methylprednisolone 250 or 500 mg every 6 hours for 3 to 7 days.[7] Another study found oral prednisone alone (1 mg/kg daily for 14 days) to be ineffective whereas intravenous methylprednisolone (1 g daily for 3 days) followed by oral prednisone (1 mg/kg daily for 11 days) was beneficial in the treatment of acute optic neuritis.[8] Unexpectedly, there was an increased risk of new episodes in patients treated with oral prednisone alone,[8] and this regimen should be avoided.[9] A review of corticosteroid use in optic neuritis concluded that high-dose oral or parenteral methylprednisolone, or corticotropin, were of value in the treatment of acute disease. However, their long-term benefit could not be determined.[10] In contrast, a systematic review of 5 studies found no evidence of benefit from intravenous or oral corticosteroid therapy at the doses used.[11]

1. Van Stavern GP, Newman NJ. Optic neuropathies: an overview. *Ophthalmol Clin North Am* 2001; 14: 61–71.
2. Purvin VA. Optic neuropathies for the neurologist. *Semin Neurol* 2000; 20: 97–110.
3. Arnold AC. Ischemic optic neuropathies. *Ophthalmol Clin North Am* 2001; 14: 83–98.
4. Eggenberger ER. Inflammatory optic neuropathies. *Ophthalmol Clin North Am* 2001; 14: 73–82.
5. Hickman SJ, *et al.* Management of acute optic neuritis. *Lancet* 2002; 360: 1953–62.
6. Kupersmith MJ, *et al.* Autoimmune optic neuropathy: evaluation and treatment. *J Neurol Neurosurg Psychiatry* 1988; 51: 1381–6.
7. Spoor TC, Rockwell DL. Treatment of optic neuritis with intravenous megadose corticosteroids: a consecutive series. *Ophthalmology* 1988; 95: 131–4.
8. Beck RW, *et al.* A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. *N Engl J Med* 1992; 326: 581–8.
9. Balcer LJ. Optic neuritis. *N Engl J Med* 2006; 354: 1273–80.
10. Kaufman DI, *et al.* Practice parameter: the role of corticosteroids in the management of acute monosymptomatic optic neuritis: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2000; 54: 2039–44.
11. Vedula SS, *et al.* Corticosteroids for treating optic neuritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 20/03/07).

Organ and tissue transplantation

For a discussion of organ and tissue transplantation, including the role of corticosteroids, see p. 1932.2.

Osteoarthritis

Systemic corticosteroids are not considered to have a place in the management of osteoarthritis (p. 12.3); however, intra-articular injection may be useful for acute exacerbations of joint pain and inflammation. Such injections should be given only infrequently and as adjunctive therapy.

Osteopetrosis

Osteopetrosis is a rare set of heterogeneous disorders characterised by an increase in bone density, generally due to a failure of the osteoclasts to resorb mineralised bone. In the severe infantile malignant form there is reduction in the bone marrow space, leading to anaemia, hepatosplenomegaly, and nerve compression that may produce blindness and deafness; early death often results. The adult form is benign; patients typically present with fractures, back and bone pain, but no haematological abnormalities, and generally have a full life expectancy.[1]

Bone marrow transplantation may be curative for the infantile malignant form if a suitable donor can be found.[1,2] Corticosteroids are used palliatively. Benefit has been reported in 3 of 4 children treated with oral prednisone 1 mg/kg daily, with phosphate supplements and a low-calcium diet.[3] Some patients have also benefited from the use of high-dose calcitriol, again with a low-calcium diet.[4]

Another study, in 14 patients, found that treatment with interferon gamma-1b increased bone resorption.[5] In 11 who received this treatment for 18 months there was stabilisation or improvement in clinical condition and a reduction in the frequency of serious infection.

1. Kocher MS, Kasser JR. Osteopetrosis. *Am J Orthop* 2003; 32: 222–8.
2. Gerritsen EJ, *et al.* Bone marrow transplantation for autosomal recessive osteopetrosis: a report from the Working Party on Inborn Errors of the European Bone Marrow Transplantation Group. *J Pediatr* 1994; 125: 896–902.
3. Dorantes LM, *et al.* Juvenile osteopetrosis: effects on blood and bone of prednisone and a low calcium, high phosphate diet. *Arch Dis Child* 1986; 61: 666–70.
4. Key LL, Ries WL. Osteopetrosis: the pharmaco-physiologic basis of therapy. *Clin Orthop* 1993; 294: 85–9.
5. Key LL, *et al.* Long-term treatment of osteopetrosis with recombinant human interferon gamma. *N Engl J Med* 1995; 332: 1594–9.

Pain

Corticosteroids have produced improvement, often substantial, in neuropathic pain, including pain due to nerve damage and sympathetically maintained pain, and are widely used in conditions such as cancer pain. Dexamethasone, methylprednisolone, and prednisolone have been used for pain management, sometimes in the form of long-acting depot injections administered locally. The exact mechanism of action of corticosteroids in analgesia is not clear but may involve relief of pressure on nervous tissue by reduction of inflammation and oedema.

For discussions of pain and its management, see p. 4.1.

Pancreatitis

Although corticosteroids are generally ineffective for pancreatitis (p. 2580.2), auto-immune pancreatitis is one form of the disease that does respond well to corticosteroid therapy. An oral dose of prednisolone (or prednisone) 30 to 40 mg daily may be used for control of the initial inflammatory phase.[1,2] The dose is then gradually reduced, although the optimal duration of treatment and the role of low-dose maintenance therapy is not yet clear.[2] Responses to corticosteroids have also been reported[3,4] in patients with acute episodes of pancreatitis caused by sarcoidosis (p. 1612.2).

1. Finkelberg DL, *et al.* Autoimmune pancreatitis. *N Engl J Med* 2006; 355: 2670–6.
2. Pannala R, Chari ST. Corticosteroid treatment for autoimmune pancreatitis. *Gut* 2009; 58: 1438–9.
3. McCormick PA, *et al.* Pancreatitis in sarcoidosis. *BMJ* 1985; 290: 1472–3.
4. Limaye AP, *et al.* Sarcoidosis associated with recurrent pancreatitis. *South Med J* 1997; 90: 431–3.

Pemphigus and pemphigoid

Systemic corticosteroids are the mainstay of management of pemphigus and pemphigoid (p. 1687.1). Initially, high doses are used to control blistering, which may take weeks. The optimum dose has not yet been established and suggestions have varied enormously; very high doses of oral prednisolone have been used in the past. The usual starting dose for widespread disease is about 1 mg/kg daily of prednisolone, continued until new blisters stop forming, then gradually decreased. However, doses above 750 micrograms/kg daily may have no additional benefit in bullous pemphigoid, and lower starting doses have been suggested for some patients: 300 micrograms/kg daily in localised or mild disease, 600 micrograms/kg daily in moderate disease, and 0.75 to 1 mg/kg daily in severe disease.[1] Doses of 40 to 60 mg daily for mild pemphigus vulgaris and 60 to 100 mg daily for more severe disease have been recommended.[2] Pulsed intravenous corticosteroids such as methylprednisolone (0.25 to 1 g given for up to 5 consecutive days) may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2] Other immunosuppressants may be added once remission is achieved and the condition has stabilised, with the aim of tapering the corticosteroid and eventually withdrawing treatment. Maintenance treatment must be individualised; one suggested regimen for tapering the corticosteroid is to reduce the dose of prednisolone by 50% every 2 weeks; alternatively, the dose is reduced by 5 to 10 mg weekly then more slowly below 20 mg daily.[2]

A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid, and can be a useful adjunct to systemic treatment in pemphigus and pemphigoid.[1,2] A large randomised study[3] found that topical application of 40 g of clobetasol propionate cream 0.05% daily to the entire body had a similar efficacy to oral prednisone 500 micrograms/kg daily for moderate bullous pemphigoid and was better than 1 mg/kg daily for severe disease. Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations such as mouthwashes, adhesive pastes, lozenges, or aerosols.[2,4] Intralesional injections have also been used for isolated lesions of the oral mucosa.[4] Topical corticosteroids do not control ocular disease on their own but may be added to initial systemic therapy to control acute ocular inflammation; they should not be used as long-term therapy.[5]

1. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; 147: 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 12/04/10)
2. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; 149: 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 12/04/10)
3. Joly P, *et al.* A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; 346: 321–7.
4. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; 6: 93–103.
5. Laforest C, *et al.* Autoimmune bullous diseases: ocular manifestations and management. *Drugs* 2005; 65: 1767–79.

Pneumocystis pneumonia

The management of pneumocystis pneumonia (p. 567.2) is mainly with co-trimoxazole. In patients with severe infection who are hypoxic, adjuvant therapy with high-dose oral or intravenous corticosteroids reduces both the risk of respiratory failure and the risk of death.[1,2] Concerns about the potential for further immunosuppression with such adjuvant therapy in patients with HIV infection[3] do not seem to have been borne out: a comparative study noted no increase in mortality or the risk of developing other opportunistic infections.[4]

1. Miller RF, *et al.* Pneumocystis carinii infection: current treatment and prevention. *J Antimicrob Chemother* 1996; 37 (suppl B): 33–53.
2. Bye MR, *et al.* Markedly reduced mortality associated with corticosteroid therapy of Pneumocystis carinii pneumonia in children with acquired immunodeficiency syndrome. *Arch Pediatr Adolesc Med* 1994; 148: 638–41.
3. Nelson MR, *et al.* Treatment with corticosteroids—a risk factor for the development of clinical cytomegalovirus disease in AIDS. *AIDS* 1993; 7: 373–8.
4. Gallant JE, *et al.* The effect of adjunctive corticosteroids for the treatment of Pneumocystis carinii pneumonia on mortality and subsequent complications. *Chest* 1998; 114: 1258–63.

Polyarteritis nodosa and microscopic polyangiitis

Polyarteritis nodosa is considered the prototype of systemic necrotising vasculitis. It may occur at any age but is more common in white patients and in men. It is characterised by inflammation throughout the arterial wall with fibrinoid necrosis of the arterial media, particularly in medium-sized vessels, partial occlusion of the vessel due to proliferation of the intima (possibly leading to thrombosis and infarction), fibrosis, and the formation of aneurysms. Microscopic polyangiitis, in which small vessels are mainly involved, with frequent renal and pulmonary involvement, has been seen as part of the spectrum of polyarteritis nodosa but is now considered an entity in its own right, although patients may have features of both. Antineutrophil cytoplasmic antibodies (ANCA) are common in patients with microscopic polyangiitis, which has many similarities to Wegener's granulomatosis (p. 1615.2), but not in classic polyarteritis nodosa.

Symptoms depend on the vessels affected but most patients have fever, weight loss, myalgia, and arthralgia. Those associated with gastrointestinal involvement include mouth ulceration, diarrhoea, visceral pain, haemorrhage, or sometimes infarction of the bowel, while involvement of liver can lead to hepatomegaly or hepatic necrosis and pancreatic involvement may simulate pancreatitis. Renal involvement may present as acute glomerulonephritis and renal failure or as nephrotic syndrome; like pulmonary involvement it is a feature particularly of microscopic polyangiitis, and associated with a poor prognosis. Skin lesions, peripheral neuropathies, alterations in mental function, convulsions, episcleritis or scleritis and retinal vasculitis, ischaemic heart disease, heart failure, Raynaud's phenomenon, and hypertension are among other potential symptoms. If untreated, death, usually due to renal or cardiac involvement, occurs in about 90% of patients within 5 years.

Classic polyarteritis nodosa may respond to treatment with a corticosteroid given alone, typically prednisone or prednisolone in a dose of 40 to 60 mg daily; however, although the benefits of adding a cytotoxic to the regimen have been queried,[1,2] a combined regimen with cyclophosphamide is often preferred.[1,3–5] Some reserve combined therapy for patients with evidence of more severe disease.[6] In patients with microscopic polyangiitis a combined regimen is recommended.[6,7] One suggested oral regimen is prednisone or prednisolone 1 mg/kg with cyclophosphamide 2 mg/kg, both daily, for initial induction of remission.[8] Pulsed intravenous methylprednisolone has also been used, followed by a tapering dose of corticosteroid. There is a trend towards giving shorter courses of cyclophosphamide, and to using intravenous pulsed cyclophosphamide rather than oral dosage, in an attempt to reduce adverse effects.[5,8,9] Treatment with corticosteroids and cyclophosphamide should not exceed 1 year.[9] Azathioprine has been substituted for cyclophosphamide to maintain remission, and mycophenolate mofetil has been tried in a few patients as an alternative to cyclophosphamide in combination therapy after initial induction.[6,10] Rituximab plus corticosteroids has been reported to have similar efficacy to cyclophosphamide plus corticosteroids, with some suggestion that rituximab may be more effective in relapsing disease.[11]

Polyarteritis nodosa may be associated with hepatitis B infection; the vasculitis responds in most cases to treatment with antiviral drugs and plasma exchange.[3,9] Prolonged treatment with corticosteroids and cyclophosphamide should be avoided in these patients because of the risks of enhanced viral replication. However, corticosteroids may be given initially to rapidly control severe life-threatening vasculitis. The corticosteroid is stopped abruptly after 2 weeks to enhance immunological clearance of hepatocytes infected by hepatitis B virus and to favour seroconversion, and plasma exchange and antiviral drug therapy are started.[3]

Plasma exchange with cyclophosphamide may also be useful in patients with microscopic polyangiitis, particularly those with acute renal failure or severe pulmonary haemorrhage.[7] Another therapy that has been tried in this group, but with ambiguous results, is high dose intravenous normal immunoglobulin.[8]

Vasodilators such as calcium-channel blockers, inhibitors of platelet activation, or drugs that improve blood flow may be useful to improve local ischaemia.[12] Skin lesions in a patient with cutaneous polyarteritis nodosa have reportedly responded to oral pentoxifylline.[13]

1. Taylor HG, Samanta A. Treatment of vasculitis. *Br J Clin Pharmacol* 1993; 35: 93–104.
2. Conn DL. Role of cyclophosphamide in treatment of polyarteritis nodosa? *J Rheumatol* 1991; 18: 489–90.
3. Guillevin L, *et al.* Treatment of polyarteritis nodosa and Churg-Strauss syndrome: a meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. *Ann Med Interne (Paris)* 1992; 143: 405–16.
4. Guillevin L, *et al.* Longterm follow up after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange: a prospective randomized trial of 71 patients. *J Rheumatol* 1991; 18: 567–74.
5. Colmegna I, Maldonado-Cocco JA. Polyarteritis nodosa revisited. *Curr Rheumatol Rep* 2005; 7: 288–96.
6. Guillevin L, Pagnoux C. When should immunosuppressants be prescribed to treat systemic vasculitides? *Intern Med* 2003; 42: 313–17.
7. Semple D, *et al.* Clinical review: vasculitis on the intensive care unit - part 2: treatment and prognosis. *Crit Care* 2005; 9: 193–7.
8. Savage COS, *et al.* Primary systemic vasculitis. *Lancet* 1997; 349: 553–8.
9. Guillevin L, Lhote F. Treatment of systemic vasculitides. *Adv Nephrol Necker Hosp* 1999; 29: 35–52.
10. Nowack R, *et al.* Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. *Lancet* 1997; 349: 774.
11. Stone JH, *et al.* RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; 363: 221–32.
12. Conn DL. Update on systemic necrotizing vasculitis. *Mayo Clin Proc* 1989; 64: 535–43.
13. Calderón MJ, *et al.* Successful treatment of cutaneous PAN with pentoxifylline. *Br J Dermatol* 1993; 128: 706–7.

Polychondritis

Relapsing polychondritis is a rare systemic disease that results in inflammation and destruction of cartilage in various parts of the body, most seriously in the respiratory system (e.g. nose, larynx, and trachea). Airway narrowing and obstruction due to loss of cartilaginous support results, and may be complicated by pneumonia; fatalities have resulted. Cardiovascular involvement, ocular manifestations, skin disorders, and renal disease may occur; it may also be associated with other diseases such as the vasculitic syndromes. Mild inflammation is usually treated with dapsone, colchicine, or NSAIDs. Relatively high doses of corticosteroid may improve symptoms in active disease, but do not appear to retard progression. Acute airway obstruction may be treated with high-dose intravenous pulse corticosteroids.[1,2] Methotrexate,[3] azathioprine,[1] or ciclosporin[2] may be of value in reducing corticosteroid requirements. CD4 antibodies have also been tried in refractory disease but did not prove particularly useful in clinical practice.[2] Newer biological therapies such as infliximab or etanercept have been reported to be of benefit in a few cases, but their role in the management of the disease remains to be determined.[2]

1. Letko E, *et al.* Relapsing polychondritis: a clinical review. *Semin Arthritis Rheum* 2002; 31: 384–95.
2. Gergely P, Poór G. Relapsing polychondritis. *Best Pract Res Clin Rheumatol* 2004; 18: 723–38.
3. Trentham DE, Le CH. Relapsing polychondritis. *Ann Intern Med* 1998; 129: 114–22.

Polymyalgia rheumatica

Polymyalgia rheumatica is a rheumatic disorder of uncertain aetiology. It occurs mainly in persons over 50 years of age of European, especially Scandinavian, extraction and is more common in women than in men. The disease is characterised by myalgia and severe morning stiffness in the neck and shoulder girdle and in the hips and pelvic girdle, which may spread in more advanced cases to the muscles of the thighs, chest, and arms. Stiffness and pain are worse after periods of inactivity. There may be some joint involvement; other symptoms include fatigue, weight loss, and fever, and anaemia and raised erythrocyte sedimentation rate are seen. In some patients polymyalgia rheumatica is associated with giant cell arteritis (p. 1604.2).

Treatment. Although NSAIDs may improve the symptoms of polymyalgia rheumatica they do not control the disease process, and corticosteroids are preferred;[1–5] in particular, corticosteroid therapy is essential where giant cell arteritis is present.

The usual initial oral dose is prednisolone or prednisone 10 to 20 mg daily, depending on the severity of symptoms; higher doses are needed where giant cell arteritis is also present, particularly if there are ophthalmic symptoms.[4,6] After 1 to 2 months a reduction in dosage is usually possible

provided symptoms are well controlled. Dosage reduction should be gradual;[4-6] mean maintenance dose at one year is about 5 or 6 mg daily.[1,5,6]

Maintenance therapy may need to be prolonged. Although about a third to a half of all patients may be able to have corticosteroids withdrawn within about 2 years,[2] maintenance can be required for considerably longer periods.[3,6] Intramuscular methylprednisolone has also been found to be effective in polymyalgia rheumatica; because the cumulative dose with prolonged therapy is lower it has been suggested that this has advantages over the use of oral corticosteroids.[7] Intravenous pulse methylprednisolone has also been used.[5] Relapse is not uncommon and is most likely within one year of corticosteroid withdrawal.[2,3,5] It may be associated with arteritic symptoms, but arteritic relapses are unusual in patients whose original presentation was pure polymyalgia.[2] Methotrexate or azathioprine may be used for their corticosteroid-sparing effect in patients in whom withdrawal is difficult.[2-4]

1. Kyle V. Polymyalgia rheumatica. *Prescribers' J* 1997; 37: 138–44.
2. Swannell AJ. Polymyalgia rheumatica and temporal arteritis: diagnosis and management. *BMJ* 1997; 314: 1329–32.
3. Zilko PJ. Polymyalgia rheumatica and giant cell arteritis. *Med J Aust* 1996; 165: 438–42.
4. Salvarani C, *et al.* Polymyalgia rheumatica. *Lancet* 1997; 350: 43–7.
5. Gran JT. Current therapy of polymyalgia rheumatica. *Scand J Rheumatol* 1999; 28: 269–72.
6. Matteson EL, Bird HA. Polymyalgia rheumatica and giant cell arteritis. In: Adebajo A, ed. *ABC of rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 107–13.
7. Dasgupta B, *et al.* An initially double-blind controlled 96 week trial of depot methylprednisolone against oral prednisolone in the treatment of polymyalgia rheumatica. *Br J Rheumatol* 1998; 37: 189–95.

Polymyositis and dermatomyositis

The term polymyositis has been used to describe several types of rare idiopathic inflammatory muscle disorders (myopathies).

The cardinal symptom of polymyositis is symmetrical progressive muscle weakness, usually starting in the shoulder girdle and neck, and pelvic girdle. Onset is usually gradual over a period of months, and accompanied by mild pain and tenderness, although more rapidly evolving disease with intense muscle pain is known. With progression, weakness may prevent the patient from moving their limbs, and muscle atrophy and contracture can develop. Dysphagia, pulmonary aspiration, and hypoventilation may occur, and some patients develop fibrosing alveolitis; pulmonary involvement, especially aspiration pneumonia, can be fatal. ECG abnormalities, usually asymptomatic, are common, and some patients develop Raynaud's syndrome. Primary disease may be associated with rashes, in which case it is known as dermatomyositis. Purplish scaly rashes on knees, elbows, and knuckles, and a characteristic purplish ('heliotrope') coloration and oedema of the eyelids may occur. A childhood form known as juvenile dermatomyositis exists, in which additional signs include vasculitis and subcutaneous calcium deposition (calcinosis cutis), and gastrointestinal haemorrhage and perforation may occur.

Treatment. Patients with active disease require bed rest, with the head elevated in patients at risk of aspiration. Physiotherapy to maintain muscle tone and avoid the development of contractures may be required.

Initial drug therapy is based on corticosteroids.[1-5] The usual choice is oral prednisone or prednisolone 40 to 60 mg or more, or 1 to 2 mg/kg daily. This usually produces improvement within 1 to 2 months. The dose may then be gradually tapered off to the minimum required for disease control;[1-3] some patients with well controlled disease may be satisfactorily maintained on an alternate-day regimen.[2,3] In patients with severe disease or extramuscular manifestations such as lung involvement, pulse intravenous methylprednisolone may be preferred initially, to gain more rapid disease control.[1,2,4] Maintenance therapy may need to be prolonged and a reduction in corticosteroid dosage to the minimum is therefore desirable, but too early or too rapid a reduction may lead to relapse.

Up to 30% of patients do not respond to corticosteroids,[2] or develop unacceptable adverse effects, and in these cases the second-line drugs are cytotoxic immunosuppressants.[1-3] There is considerable experience with the use of methotrexate, orally, subcutaneously, intramuscularly, or intravenously, usually at weekly intervals; it may be used with corticosteroids, permitting a reduction in their dose. Azathioprine may also be given with corticosteroids, again permitting a reduction in corticosteroid dosage, and the combination has also been shown to be superior to a corticosteroid alone for long-term maintenance (although this was only apparent after more than a year of therapy).[6] There is some evidence that methotrexate may be superior to azathioprine in patients unresponsive to prednisone alone.[7] Combining methotrexate and azathioprine has also been suggested.[2,4]

Some consider that corticosteroid therapy should be combined with a cytotoxic immunosuppressant such as azathioprine or methotrexate from the outset of treatment.

The role of other drugs is less well defined. Cyclophosphamide may be of use in patients with lung disease,[1,3,5] while chlorambucil and tacrolimus have produced benefit in individual cases but have not been formally assessed.[4] There have been reports of ciclosporin producing a response in refractory disease.[2,4] Normal immunoglobulin has also produced responses; it is usually reserved for refractory cases, or as an add-on therapy in patients inadequately controlled on corticosteroids and immunosuppressants, or for whom immunosuppressants are contra-indicated.[2,3] Promising results have been obtained with fludarabine[1] and mycophenolate mofetil;[2,3] there are preliminary reports of success with etanercept, and infliximab, and interferon beta has been investigated.[2]

Cutaneous symptoms in patients with dermatomyositis do not always respond satisfactorily to corticosteroids, but hydroxychloroquine is reputed to be of benefit in patients with rash,[8] probably due to a photoprotective effect.[9] Calcinosis, which can cause considerable morbidity, is particularly difficult to treat but some cases have responded to treatment with aluminium hydroxide, alendronate, diltiazem, or magnesium sulfate.[4] Warfarin therapy has been used,[10,11] but its value for calcinosis is disputed.[12]

1. Oddis CV. Current approach to the treatment of polymyositis and dermatomyositis. *Curr Opin Rheumatol* 2000; 12: 492–7.
2. Mastaglia FL, *et al.* Inflammatory myopathies: clinical, diagnostic and therapeutic aspects. *Muscle Nerve* 2003; 27: 407–25.
3. Dalakas MC. Therapeutic approaches in patients with inflammatory myopathies. *Semin Neurol* 2003; 23: 199–206.
4. Reed AM, Lopez M. Juvenile dermatomyositis: recognition and treatment. *Pediatr Drugs* 2002; 4: 315–21.
5. Pilkington CA, Wedderburn LR. Paediatric idiopathic inflammatory muscle disease: recognition and management. *Drugs* 2005; 65: 1355–65.
6. Bunch TW. Prednisone and azathioprine for polymyositis: long-term followup. *Arthritis Rheum* 1981; 24: 45–8.
7. Joffe MM, *et al.* Drug therapy of the idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine, and methotrexate and a comparison of their efficacy. *Am J Med* 1993; 94: 379–87.
8. Woo TY, *et al.* Cutaneous lesions of dermatomyositis are improved by hydroxychloroquine. *J Am Acad Dermatol* 1984; 10: 592–600.
9. Cox NH. Amyopathic dermatomyositis, photosensitivity and hydroxychloroquine. *Br J Dermatol* 1995; 132: 1016–17.
10. Berger RG, Hadler NM. Treatment of calcinosis universalis secondary to dermatomyositis or scleroderma with low dose warfarin. *Arthritis Rheum* 1983; 26 (suppl): S11.
11. Martinez-Cordero E, *et al.* Calcinosis in childhood dermatomyositis. *Clin Exp Rheumatol* 1990; 8: 198–200.
12. Ansell B. Is there a treatment for the calcinosis of juvenile dermatomyositis? *Br J Rheumatol* 1990; 29: 263.

Polyneuropathies

Ten patients with subacute demyelinating polyneuropathy obtained a beneficial response to corticosteroid therapy.[1] In one patient the response was initially slight, but became dramatic when azathioprine was added. Prednisone was given in initial single daily doses of 40 to 150 mg, until definite clinical improvement was obtained, and followed by a single-dose alternate-day regimen. Corticosteroids are generally considered to be of little use in Guillain-Barré syndrome (see under Musculoskeletal and Nerve Disorders, p. 2406.1), which usually occurs due to an acute inflammatory polyradiculoneuropathy. In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), corticosteroids are reported to be beneficial,[1,2] although a review[2] found weak evidence to support this. Subacute demyelinating neuropathy appeared to be a distinct and clinically identifiable entity in which corticosteroid therapy is indicated.[1]

1. Oh SJ. Subacute demyelinating polyneuropathy responding to corticosteroid treatment. *Arch Neurol* 1978; 35: 509–16.
2. Mehndiratta MM, Hughes RAC. Corticosteroids for chronic inflammatory demyelinating polyradiculoneuropathy. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 12/05/05).

Postoperative ocular inflammation

Corticosteroid eye drops are used to control the inflammatory response commonly seen after cataract surgery; prednisolone is usually used but dexamethasone may be necessary if the inflammation is severe.

Corticosteroids should only be used with care and for short periods for topical control of postoperative ocular inflammation, as discussed on p. 103.3.

Pregnancy

Although some adverse effects have been recorded and certain precautions need to be observed, the use of corticosteroids during pregnancy (see under Precautions, p. 1619.1) is appropriate to promote fetal maturation where there is a risk of premature delivery (see Neonatal Respiratory Distress Syndrome, p. 1608.3). In addition, in those maternal conditions serious enough to require systemic corticosteroids the risk to both mother and offspring of discontinuing therapy is often greater than that of corticosteroid use during pregnancy.

Psoriasis

The management of psoriasis is described on p. 1688.1 where topical corticosteroids are mentioned among first-line treatments. Combination therapy using corticosteroids with other topical treatments, such as calcipotriol or tazarotene, may be used to reduce adverse effects and improve efficacy of both drugs.[1]

Intralesional injection of corticosteroids has been used for small, localised, recalcitrant plaques of psoriasis but caution is required to avoid skin atrophy or depigmentation.[2] Systemic corticosteroids are not generally recommended, but have been used for short periods in extreme or rare cases; there is a risk of systemic adverse effects and of rebound psoriasis occurring on stopping therapy.

Topical corticosteroids remain the mainstay of treatment in scalp psoriasis, although long-term treatment is not recommended; the more potent corticosteroids are reserved for adult use.[3]

1. Trozak DJ. Topical corticosteroid therapy in psoriasis vulgaris: update and new strategies. *Cutis* 1999; 64: 315–18.
2. Menter A, Barker JNWN. Psoriasis in practice. *Lancet* 1991; 338: 231–4.
3. van der Vleuten CJM, van de Kerkhof PCM. Management of scalp psoriasis: guidelines for corticosteroid use in combination treatment. *Drugs* 2001; 61: 1593–8.

Pyoderma gangrenosum

A systemic corticosteroid is one of the treatments that is usually tried in pyoderma gangrenosum (p. 1688.3). High-dose oral treatment or intravenous pulse therapy may be needed initially to induce remission.[1,2] Response is usually rapid, but maintenance doses vary considerably. Healing of superficial granulomatous pyoderma has occurred after intralesional injection of triamcinolone,[3,4] oral doses of prednisolone,[3,4] and after long-term topical corticosteroids.[4]

1. Reichrath J, *et al.* Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; 53: 273–83.
2. Brooklyn T, *et al.* Diagnosis and treatment of pyoderma gangrenosum. *BMJ* 2006; 333: 181–4.
3. Quimby SR, *et al.* Superficial granulomatous pyoderma: clinicopathologic spectrum. *Mayo Clin Proc* 1989; 64: 37–43.
4. Hardwick N, Cerio R. Superficial granulomatous pyoderma: a report of two cases. *Br J Dermatol* 1993; 129: 718–22.

Respiratory disorders

Although corticosteroids have been used in the management of many forms of respiratory disorder, this use has frequently been on an empirical and uncontrolled basis, and evidence of benefit is often somewhat mixed. Thus, while an established role exists for corticosteroids in the management of asthma (p. 1600.3), the antenatal prevention of neonatal respiratory distress syndrome (p. 1608.3), and probably in croup (p. 1603.3) they are no longer used in aspiration syndromes (p. 1804.2) and their role in interstitial lung disorders (see p. 1607.1 and under Sarcoidosis, p. 1612.2) and in acute respiratory distress syndrome (p. 1599.3) is uncertain. Other disorders in which they have been tried with varying success include bronchiolitis (p. 1601.3), chronic obstructive pulmonary disease (p. 1603.1), fat embolism syndrome,[1] acute eosinophilic pneumonia[2] and pulmonary eosinophilia,[3] diffuse alveolar haemorrhage,[4] and 'ice hockey lung' (due to nitrogen dioxide).[5]

1. Van Besouw J-P, Hinds CJ. Fat embolism syndrome. *Br J Hosp Med* 1989; 42: 304–11.
2. Anonymous. Acute eosinophilic pneumonia. *Lancet* 1990; 335: 947.
3. Anonymous. Pulmonary eosinophilia. *Lancet* 1990; 335: 512.
4. Metcalf JP, *et al.* Corticosteroids as adjunctive therapy for diffuse alveolar hemorrhage associated with bone marrow transplantation. *Am J Med* 1994; 96: 327–34.
5. Anonymous. Ice hockey lung: NO_2 poisoning. *Lancet* 1990; 335: 1191.

Retinal vasculitis

Inflammation of the retinal blood vessels (retinal vasculitis) usually occurs as a feature of ocular disorders such as Eales disease; systemic inflammatory conditions such as Behçet's disease (p. 1601.1), sarcoidosis (p. 1612.2), and multiple sclerosis (p. 996.3); or infections such as herpes (p. 955.2), tuberculosis (p. 210.2), syphilis (p. 205.2), and toxoplasmosis (p. 924.2). Vascular sheathing, occlusion, macular oedema, and retinal haemorrhage can occur, and symptoms of retinal vasculitis include painless loss of vision, blurred vision, floaters, and scotoma.[1,2]

In the treatment of non-infectious retinal vasculitis, corticosteroids are used to control inflammation and prevent long-term vision loss. Local treatment by periocular injection may be used in unilateral disease or moderate inflammation; improvement usually occurs in 2 to 3 weeks and may last for up to 3 months. Oral corticosteroids may be required for moderate to severe bilateral disease with a marked reduction in visual acuity, and improvement may take 3 to 4 weeks to appear.[1] Other immunosuppressants may be needed for vasculitis that is unresponsive or inadequately controlled by corticosteroids, and may be used for their corticosteroid-sparing effect when long-term therapy is required. Azathioprine and ciclosporin are most

commonly used, but cyclophosphamide, methotrexate, and mycophenolate have also been tried.[1,2] Appropriate anti-infective therapy can clear retinal vasculitis associated with infection, but corticosteroids may be needed where there is residual vasculitis.[1]

1. Walton RC, Ashmore ED. Retinal vasculitis. *Curr Opin Ophthalmol* 2003; 14: 413–19.
2. Levy-Clarke GA, Nussenblatt R. Retinal vasculitis. *Int Ophthalmol Clin* 2005; 45 (2): 99–113.

Retroperitoneal fibrosis

Retroperitoneal fibrosis[1–4] is a rare disease that is idiopathic in most cases, but may be secondary to other causes, such as malignancy, infection, retroperitoneal injury, or as an adverse effect of a drug. Fibrosis and inflammation develop in the retroperitoneum resulting in a peri-aortic mass; organ involvement can cause urinary-tract obstruction, bowel dysfunction, and venous compression. Most patients present with dull, poorly localised pain in the back, flank, or abdomen. Physical manifestations include hypertension, lower extremity oedema, and venous thromboembolism.

Treatment involves removal of any external cause, preservation of renal function, and suppression of the inflammatory process. Surgery is used to confirm diagnosis and also to relieve cases with severe ureteral obstruction.

Corticosteroids are the mainstay of medical therapy, although the optimal dose and duration remain to be established. Typical regimens start with a high initial dose of prednisone or prednisolone (40 to 60 mg daily) which is then gradually tapered over 2 to 3 months to a maintenance dose of 5 to 10 mg daily, and then stopped after 1 to 2 years.[1–4] Disease relapse is common after stopping corticosteroids.[1]

Immunosuppressive drugs have been used either in unresponsive cases, or as part of a corticosteroid-sparing regimen;[1,2] while no controlled studies have been done, there are anecdotal reports of efficacy using azathioprine, ciclosporin, cyclophosphamide, methotrexate, and mycophenolate mofetil.[1–4] Colchicine with a low- to moderate-dose corticosteroid for a prolonged period has been reported to be of benefit.[4] Tamoxifen monotherapy has also been reported to be effective, although results have been mixed.[1] While some have stated that its place in therapy has yet to be defined,[1,2] others consider reports of benefit to be convincing and that it is a relatively safe choice.[4] Despite a lack of data, some have advocated that the use of imatinib or rituximab be considered when other treatments have failed or prove problematic.[4]

1. Monev S. Idiopathic retroperitoneal fibrosis: prompt diagnosis preserves organ function. *Cleve Clin J Med* 2002; 69: 160–6.
2. van Bommel EFH. Retroperitoneal fibrosis. *Neth J Med* 2002; 60: 231–42.
3. Vaglio A, *et al.* Retroperitoneal fibrosis: evolving concepts. *Rheum Dis Clin North Am* 2007; 33: 803–17.
4. Swartz RD. Idiopathic retroperitoneal fibrosis: a review of the pathogenesis and approaches to treatment. *Am J Kidney Dis* 2009; 54: 546–53.

Rheumatoid arthritis

Systemic corticosteroids can play an important role in the management of juvenile idiopathic arthritis (p. 12.1); they may be given by intra-articular injection in oligoarthritis, and to control disease flares, or systemically in more widespread and severe disease.

Similarly, in adult rheumatoid arthritis (p. 13.2), corticosteroids may be added to DMARD therapy to control synovitis or provide cover when changing therapies, since they provide rapid symptomatic control. They have been shown to reduce the development of joint erosions, and in the short-term this beneficial effect outweighs their adverse effects on bone. Short- to moderate-term use of systemic corticosteroids (in doses not exceeding the equivalent of 15 mg of prednisolone daily) is therefore considered valuable. However, their adverse effects mean that longer term use cannot be justified. Intra-articular injection is recommended for acute disease flares, particularly when combined with aggressive DMARD therapy.

References.

1. Gotzsche PC, Johansen HK. Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 05/07/05).
2. Criswell LA, *et al.* Moderate-term, low-dose corticosteroids for rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1998 (accessed 12/05/05).
3. Cleary AG, *et al.* Intra-articular corticosteroid injections in juvenile idiopathic arthritis. *Arch Dis Child* 2003; 88: 192–6.
4. Luqmani R, *et al.* British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (the first two years). *Rheumatology (Oxford)* 2006; 45: 1167–9. Full guideline available at: http://rheumatology.oxfordjournals.org/cgi/data/kel215a/DC1/1 (accessed 15/02/08)
5. Kirwan JR, *et al.* Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 15/02/08).

Rhinitis

For a brief description of rhinitis and a discussion of its management including the use of corticosteroids, see p. 612.1. Reviews[1,2] including a systematic review,[1] found that intranasal corticosteroids produced greater relief of the nasal symptoms of allergic rhinitis than oral antihistamines, and there was no difference between the two treatments in relief of eye symptoms. Commonly used nasal sprays appear to have similar efficacy and adverse effect profiles,[3] and choice of therapy is probably influenced by other factors including cost[3] and patient preference.[4]

1. Weiner JM, *et al.* Intranasal corticosteroids versus oral H_1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. *BMJ* 1998; 317: 1624–9.
2. Nielsen LP, *et al.* Intranasal corticosteroids for allergic rhinitis: superior relief? *Drugs* 2001; 61: 1563–79.
3. Waddell AN, *et al.* Intranasal steroid sprays in the treatment of rhinitis: is one better than another? *J Laryngol Otol* 2003; 117: 843–5.
4. Meltzer EO. Intranasal steroids: managing allergic rhinitis and tailoring treatment to patient preference. *Allergy Asthma Proc* 2005; 26: 445–51.

Sarcoidosis

Sarcoidosis is a disorder involving the development of multiple granulomas in a variety of organs, which may subsequently resolve or progress to chronic fibrosis.[1] The disease is frequently asymptomatic, and since it usually regresses spontaneously estimating the incidence is difficult, but it appears to vary considerably in different countries. It is most often seen in young adults and is slightly more common in female than male and in black than white patients.

Almost any organ can be affected, but manifestations in lymph nodes, lungs, skin, joints, and eyes are common. Lymphadenopathy, some decrease in pulmonary function, dyspnoea, and cough may mark lung and lymph node involvement. Skin manifestations include erythema nodosum, macular or papular lesions due to granuloma formation in the skin, and violaceous plaques on fingers, nose, ears, and cheeks known as lupus pernio. Arthropathy, with painful joint swellings, may be associated with erythema nodosum and fever in acute presentations; bone lesions are most common in fingers and toes. Involvement of the nervous system may be particularly difficult to diagnose because of its protean manifestations. Involvement of the eyes is usually manifest as uveitis although other symptoms include keratoconjunctivitis sicca. Symptomatic disease involving the gastrointestinal tract, liver, pancreas, heart, or kidneys is rare, although asymptomatic involvement may occur.

In addition to symptoms directly due to the disease, sarcoidosis is often associated with hypercalcaemia (p. 1776.1) and hypersensitivity to the effects of vitamin D. Other biochemical abnormalities include raised serum concentrations of angiotensin-converting enzyme (ACE), and there are abnormalities of some aspects of immune function.

Diagnosis of sarcoidosis is problematic because of its multiple manifestations and the fact that it is so often clinically silent. It is often detected by accident, when radiography is performed for other reasons, but biopsy is often needed to help confirm the disease. The Kveim test, in which an antigen derived from patients with sarcoidosis (see p. 2538.3) is given intradermally and produces a delayed reaction in patients with the disease, is now rarely used because of its perceived lack of precision, although some still consider it useful.[2]

Treatment. Asymptomatic disease requires no therapy, and since spontaneous remission can occur, corticosteroids, which are the usual therapy,[1,3] are generally reserved for patients in whom the disease affects the function of a vital organ or for patients with hypercalcaemia. NSAIDs alone may be adequate to control the fever and arthropathy of acute disease. Where corticosteroids are called for a typical oral regimen is prednisolone or prednisone 30 to 40 mg daily, the dose being reduced after several weeks as the patient improves.[3–6] Therapy should be continued (at the minimum effective maintenance dose) for 6 to 24 months before any attempt is made to withdraw it.[3] Alternate-day dosage has been suggested, with 40 mg every other day as initial therapy,[7] and 5 to 10 mg every other day as maintenance.[8] There is some evidence[9] that relapse may be more likely after withdrawal of corticosteroids than in patients who do not receive corticosteroid therapy, but this may simply reflect the natural course of disease in this group. Higher initial doses of 60 to 80 mg daily of prednisone are generally used in cardiac sarcoidosis, although controversy exists as to the clinical efficacy and optimal dose and duration of corticosteroids. Treatment halts progression and improves survival, but it does not reduce the incidence of ventricular arrhythmias.[10] In pulmonary disease, oral corticosteroids can have beneficial effects on symptoms, chest X-ray, and spirometry results in the short term (up to about 2 years) and may be used in patients with progressive disease or significant symptoms. However, there is little evidence of improved lung function and the long-term effects on disease progression are uncertain.[3,11] Inhaled corticosteroids have also been investigated for both initial and maintenance therapy in pulmonary sarcoidosis; they are not considered to be of significant benefit, although they may have a role in symptomatic relief of cough in a subgroup of patients.[3] In patients with ocular disease corticosteroid drops and ointment are used for anterior uveitis; resistant cases, or patients with posterior uveitis, require systemic corticosteroids.[1] Skin lesions usually respond to corticosteroids but the high doses that may be required for suppression of lupus pernio may produce changes in appearance as disfiguring as the disease.[4]

Other drugs have occasionally been used in sarcoidosis but are very much second-line. In patients in whom corticosteroids are not effective or not tolerated cytotoxic immunosuppressants have been given, with variable results.[1,3,4,6,8] Methotrexate has perhaps been most useful, having been found to be effective in low oral doses (up to 15 mg weekly) in refractory disease;[1,3,12] corticosteroid-sparing effects may be evident after 6 months.[8] Azathioprine has been used for severe refractory cases.[6] Results with ciclosporin have been variable,[8] although there are reports of response in refractory skin lesions and optic neuropathy.[1] Toxicity and concerns about carcinogenesis limit the use of chlorambucil and cyclophosphamide.[1,6] The antimalarials have also been tried as adjuncts or alternatives to corticosteroid therapy,[6] and may be useful for skin disease and hypercalcaemia.[8] Potential ocular toxicity is a concern, however, and although hydroxychloroquine may be less oculotoxic than chloroquine,[8] regular ophthalmological assessment is recommended.[6] Other reports of benefit in cutaneous sarcoidosis have involved allopurinol,[13] thalidomide,[14] and tranilast,[15] while there is report of response to melatonin in 2 patients with refractory sarcoidosis.[16] Infliximab and pentoxifylline have also shown promising results.[8]

1. Newman LS, *et al.* Sarcoidosis. *N Engl J Med* 1997; 336: 1224–34. Correction. *ibid.*; 337: 139.
2. Zajicek JP, *et al.* Central nervous system sarcoidosis—diagnosis and management. *Q J Med* 1999; 92: 103–17.
3. Wells AU, *et al.* Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008; 63 (suppl V): v1–v58. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/DPLD/Guidelines/Thorax%20Sept%2008.pdf (accessed 21/04/10)
4. Muthiah MM, Macfarlane JT. Current concepts in the management of sarcoidosis. *Drugs* 1990; 40: 231–7.
5. Judson MA. An approach to the treatment of pulmonary sarcoidosis with corticosteroids: the six phases of treatment. *Chest* 1999; 115: 1158–65.
6. Gibson GJ. Sarcoidosis: old and new treatments. *Thorax* 2001; 56: 336–9.
7. DeRemee RA. Sarcoidosis. *Mayo Clin Proc* 1995; 70: 177–81.
8. Baughman RP, *et al.* Sarcoidosis. *Lancet* 2003; 361: 1111–18.
9. Gottlieb JE, *et al.* Outcome in sarcoidosis: the relationship of relapse to corticosteroid therapy. *Chest* 1997; 111: 623–31.
10. Doughan AR, Williams BR. Cardiac sarcoidosis. *Heart* 2006; 92: 282–8.
11. Paramothayan NS, *et al.* Corticosteroids for pulmonary sarcoidosis. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 12/07/05).
12. Baughman RP, Lower EE. A clinical approach to the use of methotrexate for sarcoidosis. *Thorax* 1999; 54: 742–6.
13. Brechtel B, *et al.* Allopurinol: a therapeutic alternative for disseminated cutaneous sarcoidosis. *Br J Dermatol* 1996; 135: 307–9.
14. Baughman RP, *et al.* Thalidomide for chronic sarcoidosis. *Chest* 2002; 122: 227–32.
15. Yamada H, *et al.* Treatment of cutaneous sarcoidosis with tranilast. *J Dermatol* 1995; 22: 149–52.
16. Cagnoni ML, *et al.* Melatonin for treatment of chronic refractory sarcoidosis. *Lancet* 1995; 346: 1229–30.

Sciatica

For mention of the use of epidural corticosteroid injections to treat sciatica, and doubts about the extent of benefit, see Administration, Epidural Route, p. 1598.3.

Scleritis

Scleritis and episcleritis are inflammatory diseases of the sclera often associated with various systemic diseases. Episcleritis tends to be a benign superficial condition but treatment can be difficult and it tends to recur. The use of topical corticosteroids and topical NSAIDs are sometimes of temporary benefit. Scleritis is a rarer more deep-seated inflammation. Initial treatment of non-necrotising scleritis is with NSAIDs; high dose systemic corticosteroids (usually oral prednisone or prednisolone 60 to 80 mg daily) have been used successfully in many patients unresponsive to NSAIDs.[1,2] If necessary, to reduce any attendant adverse effects, corticosteroids have been given by orbital floor injection (methylprednisolone acetate 40 mg)[1] or at a reduced systemic dosage with an additional immunosuppressant such as ciclosporin, methotrexate, cyclophosphamide, or azathioprine.[3] Immunosuppressants may also be of value alone in severe or unresponsive disease.[4] It has been suggested that immunosuppressant therapy should be the initial choice in necrotising scleritis, as therapeutic failure is very common with less aggressive regimens.[4]

1. Hakin KN, *et al.* Use of orbital floor steroids in the management of patients with unilocular non-necrotising scleritis. *Br J Ophthalmol* 1991; 75: 337–9.
2. Hakin KN, *et al.* Use of cyclosporin in the management of steroid-dependent non-necrotising scleritis. *Br J Ophthalmol* 1991; 75: 340–1

3. Jabs DA, *et al.* Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000; 130: 492–513.
4. Sainz de la Maza M, *et al.* An analysis of therapeutic decision for scleritis. *Ophthalmology* 1993; 100: 1372–6.

Scleroderma

Corticosteroids may be useful for the management of scleroderma (p. 1938.3), but must be used with care because of the risk of exacerbating renal and other problems.

Seborrhoeic dermatitis

Topical corticosteroids are used with an imidazole antifungal in the management of seborrhoeic dermatitis (p. 1689.1).

Septic shock

The role of corticosteroids in septic shock (see under Septicaemia, p. 203.2) has been controversial. Early studies reported both beneficial[1] and detrimental[2] effects, but corticosteroids were considered ineffective[2,3] and likely to worsen secondary infection.[4-6] More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who have adrenal insufficiency.[7] However, their routine use in septic shock is not recommended[8] and a systematic review[9] concluded that short-course high-dose corticosteroids did not alter mortality rates in severe sepsis and septic shock, and that current evidence did not support their use. However, meta-analyses and reviews[9-11] suggest that longer courses (5 to 11 days) of low-dose corticosteroids might reduce mortality, especially in those with vasopressor-dependent septic shock.

1. Sprung CL, *et al.* The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. *N Engl J Med* 1984; 311: 1137–43.
2. Bone RC, *et al.* A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med* 1987; 317: 653–8.
3. The Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. *N Engl J Med* 1987; 317: 659–65.
4. Anonymous. No evidence that corticosteroids help in septic shock. *Drug Ther Bull* 1990; 28: 74–5.
5. Rackow EC, Astiz ME. Pathophysiology and treatment of septic shock. *JAMA* 1991; 266: 548–54.
6. Cohen J, Glauser MP. Septic shock: treatment. *Lancet* 1991; 338: 736–9.
7. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med* 2003; 348: 727–34.
8. Bernard G. The International Sepsis Forum's controversies in sepsis: corticosteroids should not be routinely used to treat septic shock. *Crit Care* 2002; 6: 384–6.
9. Annane D, *et al.* Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA* 2009; 301: 2362–75.
10. Minneci PC, *et al.* Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med* 2004; 141: 47–56.
11. Butry LD, Wax RS. Role of corticosteroids in septic shock. *Ann Pharmacother* 2004; 38: 464–72.

Sickle-cell disease

A study[1] has suggested that a short course of high-dose methylprednisolone might be a useful adjunct in controlling pain in sickle-cell crisis (p. 11.1). However, the use of corticosteroids in sickle-cell disease is problematic; apart from the usual adverse effects, including the risk of exacerbating underlying infection, corticosteroid therapy has been reported to provoke sickle-cell crisis in patients with sickle C disease—see under Precautions, p. 1619.2.

1. Griffin TC, *et al.* High-dose intravenous methylprednisolone therapy for pain in children and adolescents with sickle cell disease. *N Engl J Med* 1994; 330: 733–7.

Skin disorders

For some guidelines to the use of topical application of corticosteroids in skin disorders, see under Administration, p. 1599.2. For discussion of the use of corticosteroids in individual skin disorders see under the relevant headings in this section.

Soft-tissue rheumatism

Soft-tissue rheumatism (p. 14.2) includes several conditions affecting tendons, ligaments, muscles, fascia, and joint capsules; some lesions may respond to local injections of corticosteroid, often given with a local anaesthetic. In the treatment of shoulder pain, intra-articular injection of triamcinolone acetonide was considered to be superior to physiotherapy for reducing pain in the short-term.[1] Injection of corticosteroids below the point where the clavicle joins the shoulder blade (subacromial injection) may be superior to placebo for rotator cuff disease, as may intra-articular injection for adhesive capsulitis.[2] One meta-analysis[3] found that subacromial injection produced dose dependent benefit for up to 9 months in shoulder pain associated with rotator cuff tendinitis, with a number-needed-to-treat of between 1.4 and 2.2; there was some evidence that higher doses (50 mg equivalent of prednisone or greater) were more effective. However, there has been concern over accuracy of needle placement, and the scanty evidence to guide treatment.[2,4] There is also limited evidence that oral corticosteroids may produce improvement in pain and mobility in patients with adhesive capsulitis (frozen shoulder), but this improvement may not last beyond 6 weeks.[5] In lateral epicondylitis (tennis elbow), local injections of triamcinolone acetonide with local anaesthetic improved short-term outcomes such as pain and disability, although long-term results favoured physiotherapy.[6] Another study found that short-term benefit with corticosteroid injection for epicondylitis was paradoxically reversed after 6 weeks, implying the need for caution.[7] Evidence appears to support the use of corticosteroids such as betamethasone and methylprednisolone, with local anaesthetic, in trigger finger.[4] In contrast, no benefit has been found in Achilles' tendinopathy.[4] In carpal tunnel syndrome, injection of corticosteroids produces short term benefit but has not been shown to produce better results than other treatments such as splinting in the longer term.[8] Concerns have been expressed about the lack of good studies to support the use of corticosteroids,[2,4] and some have suggested that in tendinopathies, they be reserved for chronic injuries, and that short- or moderate-acting, soluble preparations be used.[4] Tendon rupture after local corticosteroid injection may occur.[4]

See also Administration, Intra-articular Route, p. 1598.3

1. van der Windt DAWM, *et al.* Effectiveness of corticosteroid injections versus physiotherapy for treatment of painful stiff shoulder in primary care: randomised trial. *BMJ* 1998; 317: 1292–6.
2. Buchbinder R, *et al.* Corticosteroid injections for shoulder pain. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 12/05/05).
3. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *Br J Gen Pract* 2005; 55: 224–8.
4. Speed CA. Corticosteroid injections in tendon lesions. *BMJ* 2001; 323: 382–6.
5. Buchbinder R, *et al.* Oral steroids for adhesive capsulitis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 20/02/08).
6. Smidt N, *et al.* Corticosteroid injections, physiotherapy, or a wait-and-see policy for lateral epicondylitis: a randomised controlled trial. *Lancet* 2002; 359: 657–62.
7. Bisset L, *et al.* Mobilisation with movement and exercise, corticosteroid injection, or wait and see for tennis elbow: randomised trial. Abridged version: *BMJ* 2006; 333: 939–41. Full version: http://www.bmj.com/cgi/reprint/333/7575/939.pdf (accessed 08/04/08)
8. Marshall S, *et al.* Local corticosteroid injection for carpal tunnel syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 20/02/08).

Spinal cord and head injury

Spinal cord injury usually causes significant disability arising from either partial or total paralysis. The degree of disability and organ dysfunction is determined by the spinal level of the injury, and whether severance of the cord is complete or not. Patients with lesions at the level of the fourth cervical vertebra and above will almost certainly have respiratory problems or diaphragm paralysis, requiring ventilation. Spinal shock occurs almost invariably, resulting in hypotension and reduced renal perfusion, which may cause renal failure. Patients are also at risk for acute respiratory distress syndrome (p. 1599.3) and thromboembolism (p. 1273.2). Lesions above the fifth thoracic vertebra may cause autonomic dysreflexia which results in a potentially life-threatening rise in blood pressure, requiring the use of antihypertensives.[1]

Neural tissue in the spinal cord cannot regenerate and damage is considered permanent; however, some lessening of disability is possible with rehabilitation. One of the main aims in the management of spinal cord injuries is to minimise secondary damage from hypoxia, hypoperfusion and inflammation. Results of a multicentre placebo-controlled study in the USA[2] indicated that high-dose intravenous corticosteroids resulted in improvements in neurological function if given within 8 hours of spinal cord injury. Methylprednisolone was given in an initial dose of 30 mg/kg followed by 5.4 mg/kg per hour for 23 hours. A subsequent study found that although this regimen was adequate if begun within 3 hours of injury, better results were obtained by continuing methylprednisolone for 48 hours in patients in whom therapy commenced 3 to 8 hours after injury.[3,4] The lazaroid tirilazad, given for 48 hours, had some benefit in this study, although it was less effective than 48 hours of treatment with methylprednisolone in the doses used. In contrast, a systematic review found that high-dose methylprednisolone did not improve neurological function in patients, and might potentially have a deleterious effect.[5] Another review failed to find any benefit from the use of gangliosides.[6]

The longer-term management of spinal cord injuries has been reviewed.[7]

Management of traumatic head injury poses similar problems and risks to those of spinal cord trauma. The effects of corticosteroids on mortality in acute traumatic head injury had been unclear, until an international randomised study in 10 008 adults found that the risk of death from all causes within 2 weeks[8] or 6 months[9] of significant head injury was higher in the group given methylprednisolone compared with placebo. There is little evidence that tirilazad is of any value in acute traumatic brain injury,[10,11] nor for other interventions that have been suggested for this, including barbiturates,[12] calcium-channel blockers such as nimodipine (other than perhaps in a subgroup of patients with subarachnoid haemorrhage—see also p. 1455.3),[13] central stimulants such as methylphenidate or the amfetamines,[14] inhibitors of glutamate neurotransmission,[15] or hyperventilation or hyperbaric oxygen therapy.[16,17] Progesterone is under investigation.[18,19] Mannitol is widely used after severe head injury to reduce intracranial pressure (p. 1271.3), but evidence from randomised studies is limited and it is unclear whether mannitol therapy has any effect on death or disability.[20]

1. Nichols K, *et al.* Spinal cord injury—the condition and its acute management. *Hosp Pharm* 2005; 12: 91–4.
2. Bracken MB, *et al.* A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury: results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med* 1990; 322: 1405–11.
3. Bracken MB, *et al.* Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: results of the third National Acute Spinal Cord Injury Randomized Controlled Trial. *JAMA* 1997; 277: 1597–1604.
4. Bracken MB, *et al.* Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. *J Neurosurg* 1998; 89: 699–706.
5. Short DJ, *et al.* High dose methylprednisolone in the management of acute spinal cord injury—a systematic review from a clinical perspective. *Spinal Cord* 2000; 38: 273–86.
6. Chinnock P, Roberts I. Gangliosides for acute spinal cord injury. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 05/07/05).
7. Nichols K, *et al.* Spinal cord injury—medium-and long-term management. *Hosp Pharm* 2005; 12: 95–100.
8. CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004; 364: 1321–8.
9. CRASH trial collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury—outcomes at 6 months. *Lancet* 2005; 365: 1957–9.
10. Newell DW, *et al.* Corticosteroids in acute traumatic brain injury. *BMJ* 1998; 316: 396.
11. Roberts I. Aminosteroids for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).
12. Roberts I. Barbiturates for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).
13. Langham J, *et al.* Calcium channel blockers for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 12/05/05).
14. Forsyth RJ, *et al.* Monoaminergic agonists for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 22/08/08).
15. Willis C, *et al.* Excitatory amino acid inhibitors for traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 12/05/05).
16. Roberts I, Schierhout G. Hyperventilation therapy for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1997 (accessed 12/05/05).
17. Bennett MH, *et al.* Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/05/05).
18. Wright DW, *et al.* ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med* 2007; 49: 391–402.
19. Xiao G, *et al.* Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. *Crit Care* 2008; 12: R61. Available at: http://ccforum.com/content/12/2/R61 (accessed 18/06/10)
20. Wakai A, *et al.* Mannitol for acute traumatic brain injury. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 29/04/08).

Spondyloarthropathies

Intra-articular injections of corticosteroids have been given in ankylosing spondylitis (see Spondyloarthropathies, p. 14.3).

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an auto-immune disease of complex aetiology characterised by autoantibodies that participate in the mediation of tissue damage affecting joints, skin, kidney, CNS, and other organs. It is far more common in women than in men, the evidence suggesting that male hormones have a protective effect, and peak onset is usually in women in their 20s and 30s.

The commonest symptom in patients with SLE is arthralgia or arthritis; fatigue, fever, weight loss, rashes (characteristically a so-called 'butterfly rash' on the cheeks and bridge of the nose), CNS involvement including personality changes, anaemia, nephritis, and pulmonary symptoms (notably pleurisy) are also frequent, while other symptoms include myalgia, alopecia, Raynaud's syndrome, convulsions, coma, stroke, pneumonitis, pericarditis, myocarditis with tachycardia, leucopenia, thrombocytopenia, coagulation disorders (both thrombosis and haemorrhage), hepatomegaly, splenomegaly, and lymphadenopathy. Thrombotic symptoms and recurrent miscarriage may represent an 'antiphospholipid antibody syndrome'

due to antibodies against phospholipids, which occurs in about a third of all patients with SLE but may also occur independently.[1,2]

Management. SLE is characterised by exacerbation and remission so individualised management with careful monitoring and appropriate and timely symptomatic treatment is required. Treatment is largely empirical and there have been few controlled studies.

In addition to any specific treatment, patients require emotional support, extensive rest, and avoidance where possible of stimuli that may provoke disease exacerbation, including ultraviolet light, certain drugs or foods rich in psoralens, infections, and psychological stress.

Mild disease may require no treatment, or may be managed simply with NSAIDs for muscular and joint symptoms.[3] In more severe, but non-life-threatening disease chloroquine or, more often, hydroxychloroquine is effective, particularly for cutaneous and joint manifestations,[4-6] although disease flare may occur on withdrawal.[7] Retinoids such as acitretin have also been shown to be of use in some patients.[8]

Many patients require treatment with corticosteroids at some point, although in such patients they can be a major cause of morbidity.[6,9] It is usual to use a corticosteroid when treatment with NSAIDs or antimalarials has failed, or when life or vital organs are threatened.[3] They are usually given in high doses (1 mg/kg or more of prednisone or prednisolone daily, sometimes preceded by a course of intravenous methylprednisolone)[3] for life-threatening manifestations such as high fever, severe thrombocytopenia, coma, seizures, or involvement of a major organ such as the kidney (see also Lupus Nephritis, below). Non-life-threatening symptoms that fail to respond to other measures will usually respond to lower corticosteroid doses (not more than 500 micrograms/kg daily of prednisolone or prednisone).[3] Once a response is achieved the dose should be tapered to the lowest required to control symptoms, sometimes in the form of alternate-day dosage, although disease may relapse.[3] Complete withdrawal is optimal, although some patients may need long-term maintenance on about 5 mg daily.[3] One study found that raising the maintenance corticosteroid dose temporarily to counteract any increases in the concentration of antibodies to double-stranded DNA may reduce the number of relapses,[10] but the design and conclusions of this study are open to criticism.

Prolonged corticosteroid therapy, particularly at the higher doses, is associated with adverse effects such as aseptic bone necrosis and an increased susceptibility to infection, and other drugs have been added to corticosteroid therapy in an attempt to lower the corticosteroid dose but maintain disease control. In particular the immunosuppressant azathioprine has been used for its corticosteroid-sparing effect.[3] Oral or intravenous pulse cyclophosphamide has been used with some success to treat severe organ involvement although toxicity may be of concern.[3,6] Low-dose weekly methotrexate may also be helpful in patients with cutaneous or joint involvement.[11] Leflunomide and tacrolimus are sometimes used in patients who are intolerant or resistant to other immunosuppressants,[6] and belimumab appears to be of benefit.[12] The antimalarials may also be combined with corticosteroid therapy, and in addition to a corticosteroid-sparing effect there is a suggestion that hydroxychloroquine may counter the adverse effects of corticosteroids on serum-lipid profiles.[3,13] Prasterone is under investigation for the treatment of severe disease.[14] Thalidomide has been investigated for treating cutaneous manifestations of SLE.[15] Remission has been reported in a few patients with refractory disease given rituximab.[5]

Thrombotic symptoms due to antiphospholipid antibodies require adequate long-term anticoagulation with warfarin or low-dose aspirin, and it should be borne in mind that stroke and related CNS symptoms will not respond to corticosteroids. In patients with other severe CNS symptoms that fail to respond to corticosteroids intravenous cyclophosphamide may be helpful,[16,17] but response is unpredictable. Intravenous immunoglobulin has been used as an adjunct in CNS lupus,[5] although its role is unclear; it may also be used in the management of thrombocytopenic symptoms.[18]

In patients with severe and potentially fatal symptoms plasma exchange may provide temporary benefit by removing circulating antibodies.

Lupus nephritis. Renal disease is probably the best studied symptom of SLE. Almost all patients develop some renal involvement,[19] with clinical nephritis in up to 50%.[20,21] Usual manifestations of renal disease include hypertension, oedema, proteinuria or frank nephrotic syndrome, and oliguria; more severe disease is usually associated with focal or diffuse proliferative glomerulonephritis on biopsy.[20,21]

Patients with active disease (worsening renal function, proteinuria, and urinary sediment) require aggressive treatment to prevent irreversible renal damage. It is generally accepted that the use of a cytotoxic immunosuppressant with a corticosteroid is more effective than the use of corticosteroids alone in controlling nephritis and the risk of end-stage renal failure,[19,20] although corticosteroids alone may be used for less severe disease.[18]

One suggested outline for treatment in severe active disease is to begin with pulsed intravenous methylprednisolone as 3 doses of 1g daily, or prednisone or prednisolone orally (initially 0.5 to 1 mg/kg daily, gradually reduced) accompanied if necessary by cyclophosphamide or azathioprine.[21] An alternative approach is to begin therapy with intermittent intravenous cyclophosphamide,[22] which appears to be more effective than pulsed methylprednisolone[23,24] and then to maintain patients with low-dose oral prednisone plus pulsed intravenous cyclophosphamide. Azathioprine may be a useful alternative for patients who cannot tolerate cyclophosphamide;[20,21] it may be used as maintenance after cyclophosphamide induction in an attempt to reduce toxicity.[19,21] Ciclosporin has also been investigated, with preliminary results suggestive of benefit,[25,26] but has been viewed with caution because of its nephrotoxicity.[20,21] Mycophenolate mofetil has shown promising results;[27,28] some suggest it may come to replace cyclophosphamide.[5] Other drugs that have been reported to be of benefit include intravenous immunoglobulins,[20] cladribine, and fludarabine.[19] Autologous haematopoietic stem-cell transplantation (p. 1933.1) is considered feasible in SLE.[20,29]

Pregnancy. Although symptoms of SLE do not appear to be exacerbated in most patients during pregnancy,[30,31] it is considered advisable that pregnancy be deferred until the disease is in remission or controlled by therapy, since complications are more likely in active disease.[15,30] Cyclophosphamide or methotrexate are contra-indicated in pregnancy because of the risk of teratogenesis but corticosteroids, azathioprine, and hydroxychloroquine may be used if necessary;[3,4,6,32] the risks of miscarriage, still-birth, growth retardation, or preterm delivery due to the disease are considered greater than the risks to the fetus of continued therapy. The use of low-dose aspirin (75 mg daily) has been recommended in women with renal involvement or a history of pre-eclampsia or fetal growth retardation;[32] in women with antiphospholipid antibodies, low-dose aspirin with subcutaneous heparin or low-molecular-weight heparin markedly improves the live-birth rate.[1,2,15,33] The use of high-dose prednisone, with or without aspirin, to suppress antiphospholipid antibodies, while reportedly effective in some women with bad obstetric histories,[34,35] has been found by others to be of no benefit,[36] and is associated with unacceptable maternal morbidity.[37] Warfarin prophylaxis, which appears effective in other patients with the antiphospholipid antibody syndrome,[38] is unsuited to pregnant women because of the teratogenic effects of warfarin.[39]

Postpartum exacerbation is well recognised,[30,32] and some workers favour prophylactic corticosteroid cover during the puerperium. A small proportion of neonates born to mothers with lupus have a neonatal lupus syndrome,[40] manifesting most seriously as heart block which may require a permanent pacemaker.

1. Levine JS, *et al.* The antiphospholipid syndrome. *N Engl J Med* 2002; 346: 752–63.
2. Cohen D, *et al.* Diagnosis and management of the antiphospholipid syndrome. *BMJ* 2010; 340: 1125–32.
3. Anonymous. Systemic lupus erythematosus. *Drug Ther Bull* 1996; 34: 20–3.
4. Borden MB, Parke AL. Antimalarial drugs in systemic lupus erythematosus: use in pregnancy. *Drug Safety* 2001; 24: 1055–63.
5. D'Cruz DP. Systemic lupus erythematosus. *BMJ* 2006; 332: 890–4.
6. Gordon C, Ramsey-Goldman R. Systemic lupus erythematosus and lupus-like syndromes. In: Adebajo A, ed. *ABC of rheumatology*. 4th ed. Chichester: Wiley-Blackwell, 2010: 114–22.
7. The Canadian Hydroxychloroquine Study Group. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med* 1991; 324: 150–4.
8. Ruzicka T, *et al.* Treatment of cutaneous lupus erythematosus with acitretin and hydroxychloroquine. *Br J Dermatol* 1992; 127: 513–18.
9. Mills JA. Systemic lupus erythematosus. *N Engl J Med* 1994; 330: 1871–9.
10. Bootsma H, *et al.* Prevention of relapses in systemic lupus erythematosus. *Lancet* 1995; 345: 1595–9. Correction. *ibid.*; 346: 516.
11. Sato EI. Methotrexate therapy in systemic lupus erythematosus. *Lupus* 2001; 10: 162–4.
12. Navarra SV, *et al.* BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011; 377: 721–31.
13. Hodis HN, *et al.* The lipid, lipoprotein, and apolipoprotein effects of hydroxychloroquine in patients with systemic lupus erythematosus. *J Rheumatol* 1993; 20: 661–5.
14. van Vollenhoven RF. Dehydroepiandrosterone in systemic lupus erythematosus. *Rheum Dis Clin North Am* 2000; 26: 349–62.
15. Ruiz-Irastorza G, *et al.* Systemic lupus erythematosus. *Lancet* 2001; 357: 1027–32.
16. Fricchione GL, *et al.* Electroconvulsive therapy and cyclophosphamide in combination for severe neuropsychiatric lupus with catatonia. *Am J Med* 1990; 88: 442–3.
17. Neuwelt CM, *et al.* Role of intravenous cyclophosphamide in the treatment of severe neuropsychiatric systemic lupus erythematosus. *Am J Med* 1995; 98: 32–41.
18. Boumpas DT, *et al.* Systemic lupus erythematosus: emerging concepts. Part 1. *Ann Intern Med* 1995; 122: 940–50.
19. Hejaili FF, *et al.* Treatment of lupus nephritis. *Drugs* 2003; 63: 257–74.
20. Kuiper-Geertsma DG, Derksen RHWM. Newer drugs for the treatment of lupus nephritis. *Drugs* 2003; 63: 167–80.
21. Anonymous. Treat lupus nephritis according to disease presentation. *Drugs Ther Perspect* 1999; 14: 6–9.
22. Austin HA, *et al.* Therapy of lupus nephritis: controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986; 314: 614–19.
23. Boumpas DT, *et al.* Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992; 340: 741–5.
24. Gourley MF, *et al.* Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis: a randomized, controlled trial. *Ann Intern Med* 1996; 125: 549–57.
25. Pu LW, *et al.* Clinical efficacy of cyclosporin A Neoral in the treatment of paediatric lupus nephritis with heavy proteinuria. *Br J Rheumatol* 1998; 37: 217–21.
26. Tam LS, *et al.* Long-term treatment of lupus nephritis with cyclosporin A. *Q J Med* 1998; 91: 573–80.
27. Chan TM, *et al.* Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* 2000; 343: 1156–62.
28. Ginzler EM, *et al.* Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005; 353: 2219–28.
29. Traynor AE, *et al.* Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 2000; 356: 701–7.
30. Anonymous. Systemic lupus erythematosus in pregnancy. *Lancet* 1991; 338: 87–8.
31. Yell JA, Burge SM. The effect of hormonal changes on cutaneous disease in lupus erythematosus. *Br J Dermatol* 1993; 129: 18–22.
32. Hunt BJ, Lakasing L. Management of pre-existing disorders in pregnancy: connective-tissue disorders. *Prescribers' J* 1997; 37: 54–60.
33. Rai R, *et al.* Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997; 314: 253–7.
34. Lubbe WF, *et al.* Fetal survival after prednisone suppression of maternal lupus-anticoagulant. *Lancet* 1983; i: 1361–3.
35. Branch DW, *et al.* Obstetric complications associated with the lupus anticoagulant. *N Engl J Med* 1985; 313: 1322–6.
36. Laskin CA, *et al.* Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. *N Engl J Med* 1997; 337: 148–53.
37. Greaves M. Antiphospholipid antibodies and thrombosis. *Lancet* 1999; 353: 1348–53.
38. Khamashta MA, *et al.* The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med* 1995; 332: 993–7.
39. Lockshin MD. Answers to the antiphospholipid-antibody syndrome? *N Engl J Med* 1995; 332: 1025–7.
40. Anonymous. Neonatal lupus syndrome. *Lancet* 1987; ii: 489–90.

Takayasu's arteritis

Takayasu's arteritis is a vasculitis of the aorta and its branches seen particularly in young women and in Oriental patients. It is characterised by vasculitis followed by fibrosis, leading to stenosis or occlusion of the vessel. Symptoms vary depending on the anatomical site, but include constitutional symptoms such as fever, malaise, and arthralgia, syncope, dyspnoea, palpitations, loss of pulses, intermittent claudication, and visual disturbances.

Active inflammatory disease may respond to corticosteroids: doses of 1 mg/kg daily of prednisone or prednisolone, tapered after one month in patients who respond, have been suggested.[1,2] In patients who do not respond, azathioprine, cyclophosphamide, or methotrexate have been added, although opinions vary as to the necessity of cytotoxic agents in these patients.[1-3] Ciclosporin[4] and mycophenolate mofetil[5] have also been used. A preliminary report[6] suggests that the use of etanercept or infliximab to inhibit the actions of tumour necrosis factor may be useful in patients who are refractory to other treatments. Widely varying estimates of mortality and aggressiveness exist for Takayasu's arteritis, and in the absence of large controlled studies it is difficult to assess the benefits of drug therapy. The course may be very prolonged, and minimising the maintenance dosage (e.g. by alternate-day corticosteroid therapy) is important to avoid adverse effects.[7]

Surgical reconstruction of affected vessels has been carried out in patients at risk of ischaemic compromise.[8] Angioplasty has been tried.

1. Shelhamer JH, *et al.* Takayasu's arteritis and its therapy. *Ann Intern Med* 1985; 103: 121–6.
2. Sabbadini MG, *et al.* Takayasu's arteritis: therapeutic strategies. *J Nephrol* 2001; 14: 525–31.
3. Hall S, Hunder GG. Treatment of Takayasu's arteritis. *Ann Intern Med* 1986; 104: 288.
4. Horigome H, *et al.* Treatment of glucocorticoid-dependent Takayasu's arteritis with cyclosporin. *Med J Aust* 1999; 170: 566.
5. Daina E, *et al.* Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. *Ann Intern Med* 1999; 130: 422–6.
6. Hoffman GS, *et al.* And-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. *Arthritis Rheum* 2004; 50: 2296–2304.
7. Taylor HG, Samanta A. Treatment of vasculitis. *Br J Clin Pharmacol* 1993; 35: 93–104.
8. Kerr GS, *et al.* Takayasu arteritis. *Ann Intern Med* 1994; 120: 919–29.

Tuberculosis

The use of corticosteroids in tuberculosis (p. 210.2) is controversial. They should never be given to patients with active disease without protective chemotherapy cover, and must be used with caution in patients with dormant disease as it may be reactivated. Use of corticosteroids in pulmonary tuberculosis is to be avoided except in life-threatening disease. WHO suggests that corticosteroids may be useful adjuvants to antituberculous therapy in selected conditions including tuberculous meningitis, pericarditis, pleural effusion, or laryngitis, or tuberculosis of the renal tract, adrenocortical insufficiency due to adrenal gland tuber-

culosis, massive lymph node enlargement, or to control drug hypersensitivity. They are also likely to be of benefit in patients with HIV infection and the above conditions.[1] Similar recommendations have been made by NICE[2] and the CDC[3] with regard to tuberculous meningitis and pericarditis. However, systematic reviews of tuberculous pleurisy[4] and pericarditis[5] have concluded that there is insufficient evidence to support the use of corticosteroids in these conditions.

1. WHO. *TB/HIV. A clinical manual.* 2nd ed. Geneva: WHO, 2004. Available at: http://whqlibdoc.who.int/publications/2004/9241546344.pdf (accessed 06/07/06)
2. National Collaborating Centre for Chronic Conditions/NICE. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control (issued March 2011). Available at: http://www.nice.org.uk/nicemedia/live/13422/53642/53642.pdf (accessed 11/05/11)
3. American Thoracic Society, CDC, and the Infectious Diseases Society of America. Treatment of tuberculosis. *MMWR* 2003; **52** (RR-11): 1–77. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf (accessed 11/05/11) Correction. *ibid.* 2005; **53**: 1203. [dose]
4. Engel ME, *et al.* Corticosteroids for tuberculous pleurisy. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2007 (accessed 22/08/08).
5. Mayosi BM, *et al.* Interventions for treating tuberculous pericarditis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 12/05/05).

Urticaria and angioedema

Oral antihistamines are the mainstay of treatment for urticaria (p. 1689.2). Severe attacks refractory to standard therapy may require a short course of oral corticosteroid therapy.

When angioedema affecting the larynx (laryngeal oedema) is present, the patients should be treated with adrenaline as an allergic emergency (see Anaphylaxis and Anaphylactic Shock, p. 1293.2).

Uveitis

Uveitis is inflammation of the uveal tract of the eye, which comprises the choroid, ciliary body, and the iris. It is usually idiopathic but may be secondary to infection, allergy, or inflammatory disorders with an auto-immune component.

In anterior uveitis, also referred to as iridocyclitis, there is inflammation of the iris (iritis) and the ciliary body (cyclitis). It tends to be acute and self-limiting and is likely to be associated with infection. The iris becomes spongy and hyperaemic and exudates may result in adhesions between the iris and the lens (posterior synechiae). Chronic anterior uveitis is associated with formation of cataracts and glaucoma. Posterior uveitis can be acute or chronic and may just affect the choroid (choroiditis) or may also involve the retina (chorioretinitis). It is more likely to be an auto-immune condition.

The treatment of uveitis has been reviewed.[1-4]

Corticosteroids given topically and, when necessary, systemically are the mainstay of treatment for acute anterior uveitis.[5] Cycloplegics and mydriatics such as atropine, cyclopentolate, and homatropine are used adjunctively to rest the ciliary body and iris, diminish hyperaemia, and to prevent the formation of posterior synechiae. Antibacterials should be used to treat any infection. In children with chronic anterior uveitis associated with juvenile idiopathic arthritis, corticosteroids are supplemented with chronic use of an oral NSAID if inflammation persists after 90 days of treatment and attempted corticosteroid withdrawal.[6] In the 30% or so of cases that do not respond to corticosteroids and NSAIDs, low-dose weekly methotrexate (with folic acid supplements daily) is advocated, with other immunosuppressants being substituted or used adjunctively when methotrexate fails or is not tolerated.

Treatment of posterior uveitis is less satisfactory than that of acute anterior uveitis since gross damage to the retina often occurs before the condition can be controlled. Corticosteroids are usually required given either as periocular injections or as high-dose systemic therapy.[5] A suggested protocol[2] involves the use of high-dose systemic corticosteroids to control active disease; long-term control is then maintained mainly with low-dose ciclosporin, corticosteroids being tapered to a low dose or eventually withdrawn. Certain patients may require an additional immunosuppressant, usually azathioprine, although methotrexate, cyclophosphamide, ciclosporin, or chlorambucil may be considered. Other immunosuppressants being studied include tacrolimus, and there are reports of improvement with mycophenolate mofetil.[4,5]

Visual impairment in chronic uveitis is often the result of macular oedema and is not necessarily prevented by immunosuppressants. Short-term treatment with acetazolamide is considered to have produced some encouraging results in reducing chronic uveitic macular oedema but its long-term efficacy or efficacy with low-dose corticosteroids remains to be determined.[7] Although systemic and topical NSAIDs have been shown to reduce cystoid macular oedema in post cataract extraction (see Postoperative Inflammatory Ocular Disorders, p. 103.3) their role in the treatment of macular oedema associated with uveitis is less clear.

1. Anglade E, Whitcup SM. The diagnosis and management of uveitis. *Drugs* 1995; **49**: 213–23.
2. Dick AD, *et al.* Immunosuppressive therapy for chronic uveitis: optimising therapy with steroids and cyclosporin A. *Br J Ophthalmol* 1997; **81**: 1107–12.
3. McCluskey PJ, *et al.* Management of chronic uveitis. *BMJ* 2000; **320**: 555–8.
4. Becker MD, *et al.* Management of sight-threatening uveitis: new therapeutic options. *Drugs* 2005; **65**: 497–519.
5. Jabs DA, *et al.* Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000; **130**: 492–513.
6. Nguyen QD, Foster S. Saving the vision of children with juvenile rheumatoid arthritis-associated uveitis. *JAMA* 1998; **280**: 1133–4.
7. Dick AD. The treatment of chronic uveitic macular oedema: is immunosuppression enough? *Br J Ophthalmol* 1994; **78**: 1–2.

Vasculitic syndromes

Vasculitis may be defined as inflammation of the blood vessel wall, and the term has been applied in describing a wide range of diseases involving blood vessels of various sizes and types. Vasculitis may occur as part of a systemic disease such as rheumatoid arthritis or SLE, or may itself be the primary disorder, and symptoms may vary from superficial cutaneous disease, with purpura and urticaria, to progressive and fatal systemic vasculitides such as Wegener's granulomatosis. In some forms of vasculitis, such as giant cell arteritis, mononuclear giant cells may be seen, while in granulomatous vasculitis the mononuclear cells form granulomata adjacent to the damaged vessel wall. Necrotising vasculitis is used to describe inflammation associated with necrosis of the media, the middle part of the vessel wall, while polyarteritis implies inflammation of the full thickness of an arterial wall.

Because of the heterogeneous nature of this group of diseases and the degree of overlap which exists between some of them, and between them and other diseases, classification has been difficult. Classification has often been based on the size of the affected vessel, as well as the presence or absence of granulomata and antineutrophil cytoplasmic antibodies (ANCA), and whether the vasculitis is primary or secondary. Of the major primary vasculitic syndromes, giant cell arteritis (p. 1604.2) and Takayasu's arteritis (p. 1614.3) are examples of large vessel disease; classic polyarteritis nodosa (p. 1610.2) affects medium-sized vessels; Churg-Strauss syndrome (p. 1603.1), microscopic polyangiitis (p. 1610.2), and Wegener's granulomatosis (below) are diseases of small or medium-sized vessels; the so-called 'hypersensitivity vasculitides' (p. 1606.1), including Henoch-Schönlein purpura, are small vessel diseases, though usually limited in extent.

Treatment depends on the type of vasculitis, its severity, and prognosis. Treatment of the systemic vasculitides has revolved around corticosteroids and cyclophosphamide; other cytotoxic immunosuppressants, normal immunoglobulins, NSAIDs, anticoagulants, dapsone, and colchicine have been tried in various forms of disease.

Vitiligo

Topical corticosteroids are sometimes effective in inducing repigmentation in patients with vitiligo (p. 1687.2 under Pigmentation Disorders).

Wegener's granulomatosis

Wegener's granulomatosis is a form of granulomatous vasculitis that occurs more frequently in men and in white patients. It is characterised by necrotising vasculitis of small arteries and veins, accompanied by granuloma formation, and affecting particularly the respiratory tract and kidneys. It is usually associated with antineutrophil cytoplasmic antibodies (ANCA). Symptoms include rhinorrhoea, sinusitis, cough and dyspnoea (signs of pulmonary infiltration which is seen in the majority of patients at presentation); renal manifestations include haematuria, proteinuria, uraemia, and oedema of the lower limbs due to a focal glomerulonephritis which can progress to crescentic glomerulonephritis and rapidly progressive renal failure. Other organ systems may be involved, with effects similar to those of microscopic polyangiitis (see p. 1610.2). If untreated, the disease is fatal.

Treatment is with a combination regimen based on cyclophosphamide with a corticosteroid. A standard regimen has been low-dose (1 to 2 mg/kg daily) oral cyclophosphamide, with prednisolone or prednisone 1 mg/kg daily by mouth initially, subsequently tapered to an alternate-day regimen and eventually stopped.[1-3] Cyclophosphamide is usually continued for at least a year before considering gradual withdrawal but there is a trend in Europe towards the use of shorter courses of cyclophosphamide.[4] Standard treatment regimens produce improvement or remissions in about 90% of patients.[1,5] Relapses may subsequently occur in about half, and require re-treatment; prompt intensification of treatment when serum ANCA concentrations begin to rise may avert relapse.[6] There is evidence from one controlled study that addition of co-trimoxazole to maintenance regimens reduces the incidence of relapse,[7] although another suggested that it might actually increase the risk of relapse.[8]

Despite the success of regimens based on low-dose oral cyclophosphamide there is considerable concern about their toxicity, particularly since prolonged use may be necessary. Intermittent high-dose intravenous ('pulse') cyclophosphamide has been suggested as an alternative to the oral regimen with fewer adverse effects,[9] but results in practice seem to have been variable.[10,11] Regimens similar to the standard regimen, but substituting azathioprine for cyclophosphamide once remission is achieved (usually after 3 to 6 months) and continuing with low-dose corticosteroids concomitantly have been used.[12] Rituximab plus corticosteroids has been reported to have similar efficacy to cyclophosphamide plus corticosteroids, with some suggestion that rituximab may be more effective in relapsing disease.[13] Other drugs, such as methotrexate, have been tried and addition of low-dose weekly methotrexate to a corticosteroid may be a possible treatment option.[8,14-16] Ciclosporin has been reported to reverse acute renal failure in 2 patients with Wegener's granulomatosis, as well as controlling fulminant symptoms unresponsive to cyclophosphamide and corticosteroids in one of them.[17] but others have found ciclosporin plus a corticosteroid to be ineffective in suppressing disease activity.[18] Etoposide[19] and infliximab[20] have also been successfully used to induce remission in cyclophosphamide-resistant disease, but etanercept has proved ineffective in maintaining remission.[21] Other drugs that have been investigated include high-dose intravenous immunoglobulin[22] and mycophenolate mofetil.[23] While anti-CD4 monoclonal antibodies have proved useful in patients with microscopic polyangiitis, which has some similarities to Wegener's granulomatosis, the role of such investigational regimens remains to be determined.

1. Fauci AS, *et al.* Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983; **98**: 76–85.
2. Hoffman GS, *et al.* Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; **116**: 488–98.
3. Langford CA, Hoffman GS. Wegener's granulomatosis. *Thorax* 1999; **54**: 629–37.
4. Savage COS, *et al.* Primary systemic vasculitis. *Lancet* 1997; **349**: 553–8.
5. Rottem M, *et al.* Wegener granulomatosis in children and adolescents: clinical presentation and outcome. *J Pediatr* 1993;**122**: 26–31.
6. Tervaert JWC, *et al.* Prevention of relapses in Wegener's granulomatosis by treatment based on antineutrophil cytoplasmic antibody titre. *Lancet* 1990; **336**: 709–11.
7. Stegeman CA, *et al.* Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. *N Engl J Med* 1996; **335**: 16–20.
8. de Groot K, *et al.* Therapy for the maintenance of remission in sixty-five patients with generalized Wegener's granulomatosis: methotrexate versus trimethoprim/sulfamethoxazole. *Arthritis Rheum* 1996; **39**: 2052–61.
9. Cupps TR. Cyclophosphamide: to pulse or not to pulse? *Am J Med* 1990; **89**: 399–402.
10. Hoffman GS, *et al.* Treatment of Wegener's granulomatosis with intermittent high-dose intravenous cyclophosphamide. *Am J Med* 1990; **89**: 403–10.
11. Reinhold-Keller E, *et al.* Influence of disease manifestation and antineutrophil cytoplasmic antibody titre on the response to pulse cyclophosphamide therapy in patients with Wegener's granulomatosis. *Arthritis Rheum* 1994; **37**: 919–24.
12. Jayne D, *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; **349**: 36–44.
13. Stone JH, *et al.* RAVE-ITN Research Group. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med* 2010; **363**: 221–32.
14. Sneller MC. Wegener's granulomatosis. *JAMA* 1995; **273**: 1288–91.
15. Gottlieb BS, *et al.* Methotrexate treatment of Wegener granulomatosis in children. *J Pediatr* 1996; **129**: 604–7.
16. Langford CA, *et al.* Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. *Am J Med* 2003; **114**: 463–9.
17. Gremmel F, *et al.* Cyclosporin in Wegener granulomatosis. *Ann Intern Med* 1988; **108**: 491.
18. Inoue K-I, *et al.* Successful treatment with combination therapy of cyclophosphamide and cyclosporin for late recurrence of Wegener granulomatosis. *Arch Intern Med* 2000; **160**: 393–4.
19. D'Cruz D, *et al.* Response of cyclophosphamide-resistant Wegener's granulomatosis to etoposide. *Lancet* 1992; **340**: 425–6.
20. Lamprecht P, *et al.* Effectiveness of TNF-α blockade with infliximab in refractory Wegener's granulomatosis. *Rheumatology (Oxford)* 2002; **41**: 1303–7.
21. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med* 2005; **352**: 351–61.
22. Jayne DRW, *et al.* Treatment of systemic vasculitis with pooled intravenous immunoglobulin. *Lancet* 1991; **337**: 1137–9.
23. Nowack R, *et al.* Mycophenolate mofetil for systemic vasculitis and IgA nephropathy. *Lancet* 1997; **349**: 774.

Adverse Effects of Corticosteroids and their Treatment

The adverse effects of corticosteroids may result from unwanted mineralocorticoid or glucocorticoid actions, or from inhibition of the hypothalamic-pituitary-adrenal axis.

Mineralocorticoid adverse effects are manifest in the retention of sodium and water, with oedema and hypertension, and in the increased excretion of potassium

with the possibility of hypokalaemic alkalosis. In susceptible patients, cardiac failure may be induced. Disturbances of electrolyte balance are common with the naturally occurring corticosteroids, such as cortisone and hydrocortisone, but are less frequent with many synthetic glucocorticoids, which have little or no mineralocorticoid activity.

Adverse **glucocorticoid** effects lead to mobilisation of calcium and phosphorus, with osteoporosis and spontaneous fractures; muscle wasting and nitrogen depletion; and hyperglycaemia with accentuation or precipitation of the diabetic state. The insulin requirements of diabetic patients are increased. Increased appetite is often reported.

Impaired tissue repair and immune function can lead to delayed wound healing, and increased susceptibility to infection. Increased susceptibility to all kinds of infection, including septicaemia, tuberculosis, fungal infections, and viral infections, has been reported in patients on corticosteroid therapy. Infections may also be masked by the anti-inflammatory, analgesic, and antipyretic effects of glucocorticoids. The increased severity of varicella and measles may lead to a fatal outcome in non-immune patients receiving systemic corticosteroid therapy.

Other adverse effects include menstrual irregularities, amenorrhoea, hyperhidrosis, skin thinning, ocular changes including development of glaucoma and cataract, mental and neurological disturbances, benign intracranial hypertension, acute pancreatitis, and avascular necrosis of bone. An increase in the coagulability of the blood may lead to thromboembolic complications. Peptic ulceration has been reported but reviews of the literature do not always agree that corticosteroids are responsible for an increased incidence.

The negative feedback effects of glucocorticoids on the hypothalamic-pituitary-adrenal (HPA) axis may lead to adrenal atrophy, in some cases after therapy for as little as 7 days. This produces secondary adrenocortical insufficiency, which may become manifest after overly rapid withdrawal of treatment or be precipitated by some stress such as infection or trauma. Patients vary considerably in the degree and duration of adrenal suppression after a given course of corticosteroid, but adrenal atrophy may persist for months or years, and withdrawal should be gradual in those who have been treated for any length of time (see also Withdrawal, p. 1618.1). High doses of corticosteroids given during pregnancy may cause fetal or neonatal adrenal suppression. Although the precise mechanism is uncertain, growth retardation may follow the use of even relatively small doses of corticosteroids in children.

Large doses of corticosteroids, or of corticotropin, may produce Cushingoid symptoms typical of hyperactivity of the adrenal cortex, with moon-face, sometimes with hirsutism, buffalo hump, flushing, increased bruising, ecchymoses, striae, and acne (see also Cushing's Syndrome, p. 2559.1). Giving large intravenous doses of corticosteroids too rapidly may cause cardiovascular collapse.

Hypersensitivity reactions have occurred with corticosteroids, mainly when applied topically.

Adverse effects occur, in general, fairly equally with all systemic corticosteroid preparations and their incidence rises steeply if dosage increases much above physiological values, traditionally considered to be about 7.5 mg daily of prednisolone or its equivalent (see Uses and Administration, p. 1597.3, for equivalent doses of other corticosteroids). Short courses at high dosage for emergencies appear to cause fewer adverse effects than prolonged courses with lower doses.

Most topically applied (including inhaled) corticosteroids may, under certain circumstances, be absorbed in sufficient amounts to produce systemic effects. The topical application of corticosteroid preparations to the eyes has produced corneal ulcers, raised intra-ocular pressure, and reduced visual function. Application of corticosteroids to the skin has led to loss of skin collagen and subcutaneous atrophy; local hypopigmentation of deeply pigmented skins has been reported after both the intradermal injection and topical application of potent corticosteroids. Dryness, irritation, epistaxis, and rarely ulceration or perforation of the nasal septum have followed intranasal use; smell and taste disturbances may also occur. Hoarseness and candidiasis of the mouth or throat may occur in patients receiving inhaled corticosteroids.

Intrathecal dosage (including inadvertent intrathecal dosage after attempted epidural injection) has been associated with arachnoiditis.

Adverse effects should be treated symptomatically, with the corticosteroid dosage reduced or slowly withdrawn where possible.

Reviews.

1. Pardet L, *et al.* Corticosteroid-induced adverse events in adults: frequency, screening and prevention. *Drug Safety* 2007; 30: 861–81.

Adrenal suppression. The inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use may persist for a year or more after treatment is withdrawn and may cause acute adrenocortical insufficiency with circulatory collapse during stress. The degree of suppression depends on several factors, including length of treatment, time of day treatment is given, type of corticosteroid preparation used, route, dose used, and dosing interval. In general, suppression of secretion of adrenocorticotrophic hormone and atrophy of the adrenal gland become progressively more definite as doses of corticosteroid exceed physiological amounts (see Uses and Administration, p. 1597.3), and as the duration of therapy increases (significant suppression is likely in patients receiving more than 3 weeks of therapy). It is less when the corticosteroid is given as a single dose in the morning, and even less if this morning dose is given on alternate days or less frequently. In patients taking high enough doses of corticosteroids to suppress the adrenals the dose should be increased during any form of stress (for example, illness or surgery); similarly those treated with such doses within the last 2 or 3 months should be restarted on therapy. Where the interval since treatment is greater than 3 months, resumption of treatment depends on clinical assessment of signs of adrenocortical insufficiency.

To avoid precipitating acute adrenocortical insufficiency, withdrawal of corticosteroid treatment should be carried out gradually, differing regimens being used according to the disease being treated and the duration of therapy. Examples of withdrawal regimens that have been used are described under Withdrawal, p. 1618.1.

Adrenal suppression may occur after very short courses of high-dose therapy and since many patients undergoing such therapy will be under continuing stress when the drugs are stopped, gradual withdrawal of corticosteroids over 5 to 7 days is preferable.

It should also be remembered that corticosteroid-induced adrenal suppression has been associated not only with systemic therapy, but has followed topical application of corticosteroid preparations, particularly those containing potent corticosteroids. Some degree of adrenal suppression is also associated with the use of high dose inhalants and nasal preparations, and has followed the topical application of eye drops and eye ointments.

Effects on the bones and joints. Corticosteroid-induced **avascular necrosis** of bone is an uncommon but disabling complication of therapy.[1-3] The incidence may vary in patients with different disease states; alcoholics, and patients with connective tissue disease (especially SLE) may have increased susceptibility.[3,4] There may be a relationship with corticosteroid dose: even short courses of high-dose corticosteroids may be associated with its development.[1-3] Avascular necrosis has also been associated with topical application of corticosteroids.[5]

Corticosteroids may also produce **osteoporosis.** A review[6] of data obtained from studies published between 1970 and 1990 established that osteoporosis is a common consequence of long-term treatment with corticosteroids, occurring in about 50% of patients. Bone loss is more rapid during the early stages of therapy and is most rapid in areas of the skeleton containing the greatest proportion of trabecular bone such as the spine, hip, distal radius, pelvis, and ribs.

Reviews and guidelines[7-11] on the prevention and management of corticosteroid-induced osteoporosis suggest that the dose should be minimised, as oral doses above 7.5 mg of prednisolone or prednisone (or the equivalent) daily are associated with more significant bone loss and increased fracture risk.[12] Alternate-day therapy, although desirable for its reduced effect on the hypothalamic-pituitary-adrenal axis, does not reduce the risk of bone loss. It should be borne in mind that long-term use of inhaled corticosteroids may also reduce bone mineral density. Patients should maintain an adequate intake of calcium and vitamin D (prophylactic therapy with both has been advocated in all patients starting corticosteroids[13]), should take regular exercise, and avoid smoking and excessive alcohol intake. HRT has been advocated in postmenopausal women but recent re-evaluation of the risks and benefits of HRT may render this option unattractive. Bisphosphonates may be used in high-risk patients as they are effective at preventing and treating corticosteroid-induced bone loss[14] and may reduce fracture rates.[8-10] There is some evidence to suggest that calcitonin has a beneficial effect on bone mass, and it may be considered as an alternative when bisphosphonates cannot be used. Fluoride has been studied in corticosteroid-induced osteoporosis, but although it was found to increase bone density, there is concern about the resultant bone structure and a possible increase in fracture rates. There are reports of benefit from anabolic therapy, but evidence is limited. A thiazide diuretic may be helpful in controlling hypercalciuria in patients not receiving calcitriol.[8] Whether some corticosteroids have reduced effects on the bone is unclear.[9]

There is a risk of **tendinopathies** with the use of corticosteroids, especially of the Achilles and patellar tendons; ruptures have been reported.[15] Most reports have concerned oral or intra-articular use, but there have been occasional cases in patients receiving inhaled or topical corticosteroids.

1. Nixon JE. Early diagnosis and treatment of steroid induced avascular necrosis of bone. *BMJ* 1984; 288: 741–4.
2. Anonymous. Transplant osteonecrosis. *Lancet* 1985; i: 965–6.
3. Capell H. Selected side-effects: 5. steroid therapy and osteonecrosis. *Prescribers' J* 1992; 32: 32–4.
4. Knight A. Images in clinical medicine: corticosteroid osteonecrosis. *N Engl J Med* 1995; 333: 130.
5. McLean CJ, *et al.* Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet* 1995; 345: 330.
6. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990; 112: 352–64.
7. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheum* 2001; 44: 1496–1503.
8. Adachi JD, Papaioannou A. Corticosteroid-induced osteoporosis: detection and management. *Drug Safety* 2001; 24: 607–24.
9. Bone and Tooth Society, National Osteoporosis Society, and Royal College of Physicians. Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment (December 2002). Available at: http://www.rcplondon.ac.uk/pubs/books/glucocorticoid/index.asp (accessed 27/04/04)
10. Cohen D, Adachi JD. The treatment of glucocorticoid-induced osteoporosis. *J Steroid Biochem Mol Biol* 2004; 88: 337–49.
11. Saag KG. Prevention of glucocorticoid-induced osteoporosis. *South Med J* 2004; 97: 555–8.
12. van Staa TP, *et al.* Oral corticosteroids and fracture risk: relationship to daily and cumulative doses. *Rheumatology (Oxford)* 2000; 39: 1383–9.
13. Homik J, *et al.* Calcium and vitamin D for corticosteroid-induced osteoporosis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 1998 (accessed 12/05/05).
14. Homik J, *et al.* Bisphosphonates for steroid induced osteoporosis. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 1999 (accessed 12/05/05).
15. Blanco I, *et al.* Corticosteroid-associated tendinopathies: an analysis of the published literature and spontaneous pharmacovigilance data. *Drug Safety* 2005; 28: 633–43.

Effects on carbohydrate and protein metabolism. Corticosteroids produce glucose intolerance[1-4] and protein catabolism.[5,6] A population study found that *oral* corticosteroid therapy may be associated with up to 2% of incident cases of diabetes mellitus in primary care.[7] Although mainly associated with systemic use, there is a report of deterioration in diabetic control associated with high-dose *inhaled* corticosteroid treatment.[8] A study in diabetic patients also found that use of inhaled corticosteroids was associated with increased serum-glucose concentrations in a dose-response manner.[9] The risk of new-onset diabetes mellitus might also be increased with long term use of high-dose *topical* corticosteroids applied to the skin.[10]

1. Landy HJ, *et al.* The effect of chronic steroid therapy on glucose tolerance in pregnancy. *Am J Obstet Gynecol* 1988; 159: 612–15.
2. O'Byrne S, Feely J. Effects of drugs on glucose tolerance in non-insulin-dependent diabetics (part I). *Drugs* 1990; 40: 6–18.
3. Bruno A, *et al.* Serum glucose, insulin and C-peptide response to oral glucose after intravenous administration of hydrocortisone and methylprednisolone in man. *Eur J Clin Pharmacol* 1994; 46: 411–5.
4. Hurel SJ, Taylor R. Drugs and glucose tolerance. *Adverse Drug React Bull* 1995; (Oct.): 659–62.
5. Brownlee KG, *et al.* Catabolic effect of dexamethasone in the preterm baby. *Arch Dis Child* 1992; 67: 1–4.
6. Van Goudoever JB, *et al.* Effect of dexamethasone on protein metabolism in infants with bronchopulmonary dysplasia. *J Pediatr* 1994; 124: 112–18.
7. Gulliford MC, *et al.* Risk of diabetes associated with prescribed glucocorticoids in a large population. *Diabetes Care* 2006; 29: 2728–9.
8. Paul JL, *et al.* High dose inhaled corticosteroids and dose dependent loss of diabetic control. *BMJ* 1998; 317: 1491.
9. Slatore CG, *et al.* The association of inhaled corticosteroid use with serum glucose concentration in a large cohort. *Am J Med* 2009; 122: 472–8.
10. van der Linden MW, *et al.* Topical corticosteroids and the risk of diabetes mellitus: a nested case-control study in the Netherlands. *Drug Safety* 2009; 32: 527–37.

Effects on the cardiovascular system. Adverse effects of glucocorticoids include hypertension, hyperglycaemia, obesity, and dyslipidaemia,[1-3] which are independent risk factors for cardiovascular disease. However, glucocorticoids also have anti-inflammatory effects[1,2] which may exert an anti-atherosclerotic effect. Cohort studies[2,3] established that oral glucocorticoid use was associated with an increased risk for heart failure, and that high-dose therapy was associated with an increased risk for cardiovascular disease, including myocardial infarction.

1. Ng MKC, Celermajer DS. Glucocorticoid treatment and cardiovascular disease. *Heart* 2004; 90: 829–30.
2. Souverein PC, *et al.* Use of oral glucocorticoids and risk of cardiovascular and cerebrovascular disease in a population based case-control study. *Heart* 2004; 90: 859–65.
3. Wei L, *et al.* Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. *Ann Intern Med* 2004; 141: 764–70.

Effects on the cerebrovascular system. Despite being used in high doses to treat benign intracranial hypertension, corticosteroids may also occasionally cause this disorder. Children receiving long-term therapy are mainly affected, an increase in dosage often being responsible. Symptoms usually subside when dosage is reduced.[1]

1. Gibberd B. Drug-induced benign intracranial hypertension. *Prescribers' J* 1991; 31: 118–21.

Effects on the eyes. During ophthalmic use of corticosteroids about one-third of patients will develop **raised intraocular pressure**, usually within a few weeks of treatment with potent corticosteroids, or within months with weaker ones.[1] The effects on children are variable, but they may

be at risk of a greater and more rapid response to ophthalmic corticosteroids.[1] Raised intra-ocular pressure and glaucoma can also be caused by topical use of corticosteroids on the face, particularly with prolonged use.[2] There is evidence of an increased risk in patients receiving prolonged high-dose inhaled corticosteroids.[3] Increases in intra-ocular pressure appear to be less common with systemic corticosteroids,[4] but a study in elderly patients showed that the risk of raised intra-ocular pressure or open-angle glaucoma increased with the dose and duration of oral use.[5]

Topical application of corticosteroids in patients with bacterial, fungal, or viral **eye infection** can alleviate the symptoms but allow the infection to develop.[1,6] In ocular herpes simplex infection there is the risk of corneal ulceration and scarring that may lead to loss of vision.

Cataract formation is associated with systemic corticosteroid use. It has also been reported after ophthalmic[1,4] and topical[2,7] use. There is evidence that cataract formation may also be associated with prolonged use of high-dose inhaled corticosteroids.[8-10] The intranasal use of corticosteroids, however, does not appear to increase the risk.[11] It has been suggested that the lens in children might be more sensitive than in adults, but this may be due to the large doses of corticosteroids, relative to body size, given orally in these cases. Evidence of an increased risk in children from inhaled corticosteroids is limited, but is probably outweighed by the benefits of asthma control.[12]

Systemic corticosteroid use has also been associated with damage to the retinal pigment epithelial barrier, predisposing the patient to serous **retinal detachment**.[13]

1. McGhee CNJ, *et al.* Locally administered ocular corticosteroids: benefits and risks. *Drug Safety* 2002; 25: 33–55.
2. McLean CJ, *et al.* Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet* 1995; 343: 330.
3. Garbe E, *et al.* Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA* 1997; 277: 722–7.
4. Butcher JM, *et al.* Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 1994; 309: 43.
5. Garbe E, *et al.* Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. *Lancet* 1997; 350: 979–82.
6. Baratz KH, Hatenhauer MG. Indiscriminate use of corticosteroid-containing eyedrops. *Mayo Clin Proc* 1999; 74: 362–6.
7. Costagliola C, *et al.* Cataracts associated with long-term topical steroids. *Br J Dermatol* 1989; 120: 672–3.
8. Cumming RG, *et al.* Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997; 337: 8–14.
9. Garbe E, *et al.* Association of inhaled corticosteroid use with cataract extraction in elderly patients. *JAMA* 1998; 280: 539–43. Correction. *ibid.*; 1830.
10. Smeeth L, *et al.* A population based case-control study of cataract and inhaled corticosteroids. *Br J Ophthalmol* 2003; 87: 1247–51.
11. Derby L, Maier WC. Risk of cataract among users of intranasal corticosteroids. *J Allergy Clin Immunol* 2000; 105: 912–16.
12. Cumming RG, Mitchell P. Inhaled corticosteroids and cataract: prevalence, prevention and management. *Drug Safety* 1999; 20: 77–84.
13. Polak BCP, *et al.* Diffuse retinal pigment epithelopathy complicating systemic corticosteroid treatment. *Br J Ophthalmol* 1995; 79: 922–5.

Effects on the gastrointestinal tract. It has long been considered that treatment with corticosteroids might lead to peptic ulcers. Some years ago a review of the data then available suggested that since an ulcer developed in 1% of control patients not receiving corticosteroids, the 2% incidence for patients receiving corticosteroids did not warrant the prophylactic use of anti-ulcer drugs in all patients.[1] Others have found little evidence of an increased risk of peptic ulcer produced by corticosteroids alone although there is some increased risk when using them with NSAIDs.[2] A later cohort study[3] found a modest increase in risk of gastrointestinal bleeding with current use of corticosteroids, which increased when NSAIDs were also used. It has been suggested that it might be prudent to avoid such combination therapy whenever possible.[4]

Doubt has therefore been cast on the prophylactic value of anti-ulcer therapy given with corticosteroids.[1,5] If an ulcer does develop and there is good reason to continue treatment then corticosteroids may be continued along with some form of ulcer therapy.[1]

There have been several reports of corticosteroids being associated with gastrointestinal perforation.[6-9] There is a risk that the anti-inflammatory properties of corticosteroids may mask the signs of perforation and delay diagnosis with potentially fatal results.

1. Spiro HM. Is the steroid ulcer a myth? *N Engl J Med* 1983; 309: 45–7.
2. Piper JM, *et al.* Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991; 114: 735–40.
3. Nielsen GL, *et al.* Risk of hospitalization resulting from upper gastrointestinal bleeding among patients taking corticosteroids: a register-based cohort study. *Am J Med* 2001; 111: 541–5.
4. Guslandi M, Tittobello A. Steroid ulcers: a myth revisited. *BMJ* 1992; 304: 655–6.
5. Marcus P, McCauley DL. Steroid therapy and H_2-receptor antagonists: pharmacoeconomic implications. *Clin Pharmacol Ther* 1997; 61: 503–8.
6. Arsura EL. Corticosteroid-associated perforation of colonic diverticula. *Arch Intern Med* 1990; 150: 1337–8.
7. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; 66: 1164–6.
8. O'Neil EA, *et al.* Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. *Arch Dis Child* 1992; 67: 10–11.
9. Epstein A, *et al.* Perforation of colon diverticula during corticosteroid therapy for pemphigus vulgaris. *Ann Pharmacother* 1993; 27: 979–80.

Effects on growth. Corticosteroids impair normal growth in children when given systemically,[1-3] and although alternate-day therapy may reduce the effect on growth it does not abolish it. There has been some concern about possible effects of inhaled corticosteroids on growth.[1,4] Some studies have not found an effect of inhaled corticosteroids on growth if doses are modest, even when treatment is prolonged.[1,5,6] Others have found that inhaled corticosteroids, particularly in high doses, do have some effect on growth parameters,[5,7-10] but it is unclear whether this has long-term effects on the child's ultimate height, and the alternative in children requiring such high-dose therapy is likely to be an oral corticosteroid, with its consequent effects. Some studies,[11,12] in children with mild to moderate asthma, have suggested that a small reduction in growth velocity may occur in the first year of treatment, but that it then normalises and adult height is not adversely affected. Nonetheless, in the light of the increasing number of studies suggesting some effects of inhaled or intranasal corticosteroids on growth the FDA has required the inclusion of a warning in US labelling that such products may slow growth rates. For a suggestion that inhalation of a single dose of budesonide in the morning had less effect on growth than twice daily dosage, see Administration, p. 1625.2.

1. Allen DB, *et al.* A meta-analysis of the effect of oral and inhaled corticosteroids on growth. *J Allergy Clin Immunol* 1994; 93: 967–76.
2. Lai H-C, *et al.* Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *N Engl J Med* 2000; 342: 851–9.
3. Mushtaq T, Ahmed SF. The impact of corticosteroids on growth and bone health. *Arch Dis Child* 2002; 87: 93–6.
4. Hanania NA, *et al.* Adverse effects of inhaled corticosteroids. *Am J Med* 1995; 98: 196–208.
5. Wolthers OD, Pedersen S. Controlled study of linear growth in asthmatic children during treatment with inhaled glucocorticosteroids. *Pediatrics* 1992; 89: 839–42.
6. Volovitz B, *et al.* Growth and pituitary-adrenal function in children with severe asthma treated with inhaled budesonide. *N Engl J Med* 1993; 329: 1703–8.
7. Wolthers OD, Pedersen S. Short term growth during treatment with inhaled fluticasone propionate and beclomethasone dipropionate. *Arch Dis Child* 1993; 68: 673–6.
8. Todd G, *et al.* Growth and adrenal suppression in asthmatic children treated with high-dose fluticasone propionate. *Lancet* 1996; 348: 27–9.
9. McCowan C, *et al.* Effect of asthma and its treatment on growth: four year follow up of cohort of children from general practices in Tayside, Scotland. *BMJ* 1998; 316: 668–72.
10. Sharek PJ, Bergman DA. The effect of inhaled steroids on the linear growth of children with asthma: a meta-analysis. Abstract: *Pediatrics* 2000; 106: 129. Full version: http://pediatrics.aappublications.org/cgi/content/full/106/1/e8 (accessed 27/04/04)
11. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; 343: 1054–63.
12. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med* 2000; 343: 1064–9.

Effects on immune response. Owing to their immunosuppressant effect, giving corticosteroids in doses greater than those required for physiological replacement therapy is associated with increased susceptibility to infection, aggravation of existing infection, and activation of latent infection. An additional problem is that the anti-inflammatory effect of corticosteroids may mask symptoms until the infection has progressed to an advanced stage; the altered response of the body may also permit the bizarre spread of infections, frequently in aberrant forms, such as disseminated parasitic infections. The risk is greater in patients receiving high doses, or associated therapy with other immunosuppressants such as cytotoxic drugs, and in those who are already debilitated. Children receiving high doses of corticosteroids are at special risk from childhood diseases, such as chickenpox, but vaccination with living organisms is contra-indicated since infection may be induced (killed vaccines or toxoids can be given but the response may be reduced).

This increased susceptibility to infection and masking of symptoms may also be caused by topical or local corticosteroid therapy. Thus, topical application to the skin has led to unusual changes such as atypical ringworm infection. Fungal infections (particularly candidiasis), generally restricted to the mouth and throat, are associated with corticosteroid inhalations. Severe damage to the eye has followed the ocular use of corticosteroids in herpetic infections, and a generalised spread of herpes infection may follow application to the mouth in the presence of herpes infection.

Conversely, the effect of corticosteroids on the symptoms and course of some infections may be life-saving (see Infections, under Uses and Administration, p. 1606.3). Before embarking on a long-term course of corticosteroid therapy general measures for the reduction of risk of infection include a diligent search for active or quiescent infection and, where appropriate, prevention or eradication of the infection before starting, or giving chemoprophylaxis during corticosteroid treatment.

Effects on lipid metabolism. Glucocorticoids have potent effects on lipid metabolism, facilitating the effects of growth hormone and endogenous stimulants of lipolysis. As a result they increase both high- and low-density lipoprotein cholesterol concentrations in the blood.

On prolonged use glucocorticoids also have a dramatic effect on body fat distribution, resulting in the characteristic Cushingoid appearance of moon face, and increased fat at the back of the neck and supraclavicular area.

Effects on mental state. Mental disturbances caused by corticosteroids include depression, mania, euphoria, and delirium.[1,2] Psychotic symptoms, insomnia, and hyperactivity have also been reported in children and adolescents treated with inhaled,[3,4] oral, and intravenous corticosteroids.[3] The risk of adverse effects appears to be dose-related, but there are reports of cases associated with very low dosages. Reversible impairment of memory has been associated with intravenous methylprednisolone.[5-7]

1. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. *Drug Safety* 2000; 22: 111–22.
2. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc* 2006; 81: 1361–7.
3. Stuart FA, *et al.* Adverse psychological effects of corticosteroids in children and adolescents. *Arch Dis Child* 2005; 90: 500–506.
4. de Vries TW, *et al.* Reported adverse drug reactions during the use of inhaled steroids in children with asthma in the Netherlands. *Eur J Clin Pharmacol* 2006; 62: 343–6.
5. Oliveri RL, *et al.* Pulsed methylprednisolone induces a reversible impairment of memory in patients with relapsing-remitting multiple sclerosis. *Acta Neurol Scand* 1998; 97: 366–9.
6. Brunner R, *et al.* Effect of corticosteroids on short-term and long-term memory. *Neurology* 2005; 64: 335–7.
7. Uttner I, *et al.* Reversible impaired memory induced by pulsed methylprednisolone in patients with MS. *Neurology* 2005; 64: 1971–3.

Effects on the neonate. Various adverse effects have been reported in premature neonates given corticosteroids, see under Dexamethasone, p. 1633.1.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with intravenous use of dexamethasone sodium phosphate[1-4] and hydrocortisone sodium phosphate,[5] but not with hydrocortisone sodium succinate.[5] Descriptions of this reaction include itching, burning, tingling, and severe pain. It can begin within seconds of giving the injection, and clear within minutes of stopping. This reaction appears to be caused by the corticosteroid phosphate ester itself, and clears in the time it takes for the drug to be hydrolysed. It has been suggested that the reaction can be abolished or avoided by giving the drug as a dilute solution, over at least 5 to 15 minutes.[2-4]

Epidural lipomatosis (fat deposition around the spinal cord) is a rare complication of systemic corticosteroids.[6] It has been associated with both high daily doses (more than 30 mg prednisone daily) and lower doses given over several years. The onset of symptoms is usually gradual, ranging from 6 months to more than 20 years after beginning corticosteroid use. Spinal cord compression causes back pain radiating to the lower limbs, and severe neurological complications can develop. The lipomatosis may regress or disappear after the corticosteroid is withdrawn or the dose is lowered, but patients with myelopathy or rapidly progressive neurological deficit may need emergency surgery.

1. Czerwinski AW, *et al.* Effects of a single, large, intravenous injection of dexamethasone. *Clin Pharmacol Ther* 1972; 13: 638–42.
2. Allan SG, Leonard RCF. Dexamethasone antiemesis and side-effects. *Lancet* 1986; i: 1035.
3. Neff SFW, *et al.* Excruciating perineal pain after intravenous dexamethasone. *Anaesth Intensive Care* 2002; 30: 370–1.
4. Perron G, *et al.* Perineal pruritus after iv dexamethasone administration. *Can J Anesth* 2003; 50: 749–50.
5. Novak E, *et al.* Anorectal pruritus after intravenous hydrocortisone sodium succinate and sodium phosphate. *Clin Pharmacol Ther* 1976; 20: 109–12.
6. Hierholzer J, *et al.* Epidural lipomatosis: case report and literature review. *Neuroradiology* 1996; 38: 343–8.

Effects on the pancreas. Acute pancreatitis has been associated with corticosteroid use,[1-3] although evidence supporting the association has been challenged on several grounds, both clinical and experimental.[2]

1. Nakashima Y, Howard JM. Drug-induced acute pancreatitis. *Surg Gynecol Obstet* 1977; 145: 105–9.
2. Banerjee AK, *et al.* Drug-induced acute pancreatitis: a critical review. *Med Toxicol Adverse Drug Exp* 1989; 4: 186–98.
3. Feig DM, Toparian M. Corticosteroid-induced pancreatitis. *Ann Intern Med* 1996; 124: 1016.

Effects on the skin and hair. Topical corticosteroids are associated with several local adverse effects on the skin, mainly due to their antiproliferative effects on keratinocytes and fibroblasts (leading to skin thinning and atrophy), and to possible interference with the skin flora (leading to increased risk of superinfection or opportunistic infection).[1] Skin thinning is more likely if corticosteroids are applied under occlusion (this is especially true of halogenated corticosteroids, which are more resistant to inactivation by enzymes in the epidermis). Striae, which occur usually in intertriginous areas such as axillae and groin where skin is thin, moist, and occluded, are the most readily appreciable manifestation of skin atrophy,

and are irreversible, unlike more minor degrees of atrophy. Other local adverse effects include telangiectasias and purpura.[1] Acneform pustules at the site of application have occurred.

The balance between benefit and the likelihood of local or systemic adverse effects on topical application of corticosteroids will depend on the chemical structure of the drug (i.e. its lipophilicity and resistance to enzymic degradation), the formulation of the vehicle, the way in which it is applied, and the nature of the skin to be treated.[1]

Skin thinning, bruising, and purpura have also been reported in patients receiving inhaled corticosteroids.[2-4] There have been a few case reports of eczematous and erythematous lesions of the face and body, and urticaria, following inhalation or intranasal use.[5]

The adverse skin effects arising from systemic corticosteroids also include striae and skin thinning as well as acneform eruptions. Somewhat counter-intuitively a case-control study has suggested an increased risk of Stevens-Johnson syndrome or toxic epidermal necrolysis in patients receiving corticosteroids, particularly in the period shortly after beginning therapy.[6]

Hypertrichosis has occurred in patients given inhaled corticosteroid therapy, including children.[7] The risk may be increased with excessive dosage, and in some cases additional corticosteroid therapy was being given by other routes, such as intranasally or applied topically to the skin. The effect usually improved when the corticosteroid was stopped, but in some cases the excessive hair remained.

1. Mori M, *et al.* Topical corticosteroids and unwanted local effects: improving the benefit/risk ratio. *Drug Safety* 1994; 10: 406–12.
2. Shuttleworth D, *et al.* Inhaled corticosteroids and skin thinning. *Br J Dermatol* 1990; 122: 268.
3. Capewell S, *et al.* Purpura and dermal thinning associated with high dose inhaled corticosteroids. *BMJ* 1990; 300: 1548–51.
4. Tashkin DP, *et al.* Skin manifestations of inhaled corticosteroids in COPD patients: results from Lung Health Study II. *Chest* 2004; 126: 1123–33.
5. Isaksson M. Skin reactions to inhaled corticosteroids: incidence, avoidance and management. *Drug Safety* 2001; 24: 369–73.
6. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; 333: 1600–7.
7. de Vries TW, *et al.* Hypertrichosis as a side effect of inhaled steroids in children. *Pediatr Pulmonol* 2007; 42: 370–3.

Effects on the voice. Dysphonia is associated with inhaled corticosteroids.[1] Although oropharyngeal candidiasis and dysphonia may occur at the same time, many patients with dysphonia do not have candidiasis, and the two conditions do not appear to be directly related. The cause of this dysphonia has not been fully explained, but clinical investigations have found changes including bowing of the vocal cords due to bilateral adductor myopathy, mucosal changes, and supraglottic hyperfunction.

1. Lavy JA, *et al.* Dysphonia associated with inhaled steroids. *J Voice* 2000; 14: 581–8.

Hypersensitivity and anaphylaxis. There have been occasional reports of hypersensitivity reactions, and sometimes anaphylaxis, caused by corticosteroids.[1,2] Reactions have occurred with any route, although the topical route is mainly involved. It has been noted that the incidence of hypersensitivity is increasing[3] and it has been suggested that a lack of response in chronic eczema might be due to a reaction to the corticosteroid treatment.[3] Fluorinated corticosteroids may be less likely to induce a contact hypersensitivity reaction than non-fluorinated compounds.[4]

1. Kamm GL, Hagmeyer KO. Allergic-type reactions to corticosteroids. *Ann Pharmacother* 1999; 33: 451–60.
2. Torres MJ, Canto G. Hypersensitivity reactions to corticosteroids. *Curr Opin Allergy Clin Immunol* 2010; 10: 273–9.
3. Dooms-Goossens A. Sensitivity to corticosteroids: consequences for anti-inflammatory therapy. *Drug Safety* 1995; 13: 123–9.
4. Thomson KF, *et al.* The prevalence of corticosteroid allergy in two U.K. centres: prescribing implications. *Br J Dermatol* 1999; 141: 863–6.

Tumour lysis syndrome. There have been reports of corticosteroid-induced tumour lysis syndrome.[1-4]

1. Sparano J, *et al.* Increasing recognition of corticosteroid-induced tumour lysis syndrome in non-Hodgkin's lymphoma. *Cancer* 1990; 65: 1072–3.
2. Smith RE, Stoiber TR. Acute tumor lysis syndrome in prolymphocytic leukemia. *Am J Med* 1990; 88: 547–8.
3. Haller C, Dhadly M. The tumor lysis syndrome. *Ann Intern Med* 1991; 114: 808–9.
4. Tsao Y-T, *et al.* Steroids for acute spinal cord injury: revealing silent pathology. *Lancet* 2009; 374: 500.

Withdrawal of Corticosteroids

The use of pharmacological doses of corticosteroids suppresses the endogenous secretion of corticotropin by the anterior pituitary, with the result that the adrenal cortex becomes atrophied. Sudden withdrawal or reduction in dosage, or an increase in corticosteroid requirements associated with the stress of infection or accidental or surgical trauma, may then precipitate acute adrenocortical insufficiency; deaths have followed the abrupt withdrawal of corticosteroids. Adrenocortical insufficiency has also occurred after the effective reduction in systemic corticosteroid concentrations produced by overly rapid transfer from oral to inhaled corticosteroid therapy. For the emergency treatment of acute adrenocortical insufficiency caused by abrupt withdrawal of corticosteroids, see Adrenocortical Insufficiency, p. 1600.2.

In some instances, withdrawal symptoms may involve or resemble a clinical relapse of the disease for which the patient has been undergoing treatment. Other effects that may occur during withdrawal or change of corticosteroid therapy include fever, myalgia, arthralgia, weight loss, benign intracranial hypertension with headache and vomiting, and papilloedema caused by cerebral oedema. Latent rhinitis or eczema may be unmasked.

Duration of treatment and dosage are important factors in determining suppression of the pituitary-adrenal response to stress on cessation of corticosteroid treatment, and individual liability to suppression is also important.

After short courses at moderate doses it may be appropriate to withdraw corticosteroids without tapering the dose (see below). However, after high-dose or prolonged therapy, withdrawal should be gradual, the rate depending upon the individual patient's response, the dose, the disease being treated, and the duration of therapy. Recommendations for initial reduction, stated in terms of prednisolone, have varied from as little as steps of 1 mg monthly to 2.5 to 5 mg every 2 to 7 days. Provided the disease is unlikely to relapse the dose of systemic corticosteroid may be reduced rapidly to physiological values; dose reduction should then be slower to allow recovery of pituitary-adrenal function. Symptoms attributable to over-rapid withdrawal should be countered by resuming a higher dose and continuing the reduction at a slower rate. Giving corticotropin does not help to re-establish adrenal responsiveness.

This gradual withdrawal of corticosteroid therapy permits a return of adrenal function adequate for daily needs, but years may sometimes be required for the return of function necessary to meet the stress of infection, surgery, or trauma. On such occasions patients with a history of recent corticosteroid withdrawal should be protected by means of supplementary corticosteroid therapy as described under Precautions, below.

The UK CSM recommends that moderate dosage with corticosteroids (up to 40 mg daily of prednisolone, or equivalent), for up to 3 weeks, may be stopped without tapering provided that the original disease is unlikely to relapse, although prophylactic cover may be required for any stress within a week of finishing the course.[1] However, it should be borne in mind that individuals vary widely in their response to corticosteroids and their ability to tolerate withdrawal. Gradual withdrawal should be considered, even after shorter courses, if higher doses are given, or in patients with other risk factors for adrenocortical insufficiency, including those who have had repeated courses of systemic corticosteroids, those who receive a course within one year of finishing long-term corticosteroid therapy, or those who regularly take doses in the evening, when their suppressive effect is greater. Withdrawal should not be abrupt in any patient who receives systemic corticosteroids for more than 3 weeks.[1]

How dose reduction is carried out depends largely on the likelihood of relapse of the original disease. If this is unlikely, the dose of systemic corticosteroid may be reduced rapidly to physiological values (traditionally considered to be 7.5 mg of prednisolone daily or equivalent). It should then be reduced more slowly to allow the hypothalamic-pituitary-adrenal axis to recover.[1] Where disease relapse is a possibility even the initial reduction may need to be more cautious. Long-term treatment may require withdrawal over many months (such as a reduction of 1 mg in the daily dose of prednisolone every 3 to 4 weeks).

In reviews of the inhibition of hypothalamic-pituitary-adrenocortical function associated with corticosteroid use, further regimens for corticosteroid withdrawal are described.[2-4] For example, patients who have been treated for weeks or months may have their daily dose of prednisolone reduced by 2.5 to 5 mg every 2 or 3 days, or, for those on longer-term treatment, the reduction may be more gradual at a rate of 2.5 mg every 1 to 3 weeks and possibly less. When the dose has reached 10 mg daily decrements may be made with 1-mg tablets. Another approach may be to convert daily therapy gradually into alternate-day therapy by progressively reducing the amount of corticosteroid received on every second day, and once alternate-day therapy is established the dose may be further reduced until, for example, a dose of 1 mg on alternate days for one week is attained.

1. CSM/MCA. Withdrawal of systemic corticosteroids. *Current Problems* 1998; 24: 5–7. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023926&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)
2. Anonymous. Corticosteroids and hypothalamic-pituitary-adrenocortical function. *BMJ* 1980; 280: 813–14.
3. Heifer EL, Rose LI. Corticosteroids and adrenal suppression: characterising and avoiding the problem. *Drugs* 1989; 38: 838–45.
4. Page RC. How to wean a patient off corticosteroids. *Prescribers' J* 1997; 37: 11–16.

Precautions for Corticosteroids

Systemic corticosteroids should be used with great caution in the presence of heart failure, recent myocardial infarction, or hypertension, in patients with diabetes mellitus, epilepsy (but see p. 1604.1 for use in infantile spasms), glaucoma, hypothyroidism, hepatic failure, osteoporosis, peptic ulceration, psychoses or severe affective disorders, and renal impairment. Children may be at increased risk of some adverse effects; in addition, corticosteroids may cause growth retardation, and prolonged use is rarely justified. The elderly too may be at greater risk from adverse effects.

Corticosteroids are usually contra-indicated in the presence of acute infections uncontrolled by appropriate antimicrobial therapy. Similarly, patients already receiving corticosteroids are more susceptible to infection, the symptoms of which, moreover, may be masked until an advanced stage has been reached. Patients with active or doubtfully quiescent tuberculosis should not be given corticosteroids except, very rarely, as adjuncts to treatment with antitubercular drugs. Patients with quiescent tuberculosis should be observed closely and should receive chemoprophylaxis if corticosteroid therapy is prolonged.

The risks of chickenpox and probably of severe herpes zoster are increased in non-immune patients receiving therapeutic doses of systemic corticosteroids, and patients should avoid close personal contact with either infection. Passive immunisation is recommended for non-immune patients who do come into contact with chickenpox. Similar precautions apply to measles. Live vaccines should not be given to patients receiving high-dose systemic corticosteroid therapy nor for at least 3 months afterwards; killed vaccines or toxoids may be given although the response may be attenuated.

During prolonged courses of corticosteroid therapy, patients should be examined regularly. Sodium intake may need to be reduced and calcium and potassium supplements may be necessary. Monitoring of the fluid intake and output, and daily weight records may give early warning of fluid retention. Back pain may signify osteoporosis. Children are at special risk from raised intracranial pressure. Patients should carry cards (and preferably also wear bracelets) giving full details of their corticosteroid therapy; they and their relatives should be fully conversant with the implications of their therapy and the precautions to be taken.

Measures to compensate for the adrenals' inability to respond to stress (see Withdrawal, above) include increasing the dose to cover minor intercurrent illnesses or trauma such as surgery (with intramuscular doses to cover vomiting). For details of dosages used, see Uses and Administration, p. 1597.3.

Rapid intravenous injection of massive doses of corticosteroids may sometimes cause cardiovascular collapse and injections should therefore be given slowly or by infusion.

Many drugs have been reported to interfere with certain assay procedures for corticosteroids in body fluids and corticosteroids themselves may interfere with or alter the results of assays for some endogenous substances or drugs.

The risk of systemic absorption should always be considered when applying corticosteroids topically. They should not be applied with an occlusive dressing to large areas of the body. Long-term topical use is best avoided, especially in children. Also they should not be used for the treatment of ulcerative conditions, nor of rosacea, and should not be used indiscriminately for pruritus. Occasionally they may be used with the addition of a suitable antimicrobial substance in the treatment of infected skin but there is a risk of sensitivity reactions occurring.

Height should be monitored in children receiving prolonged therapy with inhaled or nasal corticosteroids. High doses of inhaled corticosteroids should preferably be inhaled using large-volume spacer devices to reduce oropharyngeal deposition and hence the incidence of candidiasis; rinsing the mouth with water after inhalation may also be helpful. In addition the use of spacer devices may reduce systemic absorption (see also Inhalation Therapy, under Uses and Administration, p. 1598.3). Paradoxical bronchospasm has occurred with inhaled corticosteroids and may require therapy to be stopped, although if mild it may be prevented by inhalation of a beta$_2$ adrenoceptor agonist, or by transfer from an aerosol to a dry powder formulation.

Caution is required when corticosteroids are used locally to treat eye disorders (see p. 1619.1).

Contraception. There are some isolated case reports of contraceptive failure in women using intra-uterine devices and receiving corticosteroid therapy.[1-3]

1. Zerner J, *et al.* Failure of an intrauterine device concurrent with administration of corticosteroids. *Fertil Steril* 1976; 27: 1467–8.
2. Inkeles DM, Hansen RI. Unexpected pregnancy in a woman using an intrauterine device and receiving steroid therapy. *Ann Ophthalmol* 1982; 14: 975.

3. Buhler M, Papiernik E. Successive pregnancies in women fitted with intrauterine devices who take anti-inflammatory drugs. *Lancet* 1983; i: 483.

Eye disorders. Topical corticosteroids have transformed the management of inflammatory disease of the anterior segment of the eye and it should be noted that while their proper use may be sight-saving their inappropriate use is potentially blinding.[1] The dangers include the conversion of a simple dendritic herpes simplex epithelial lesion into an extensive amoeboid ulcer with the likelihood of permanent corneal scarring and loss of vision and also the risk of potentiation of bacterial and fungal infections. Other dangers include the development of open-angle glaucoma and cataracts. Topical corticosteroids are used by ophthalmologists in herpes simplex keratitis but always under appropriate antiviral cover and their use requires considerable experience. They should never be given for an undiagnosed red eye and many consultant ophthalmic surgeons believe that general practitioners should never begin therapy without an ophthalmic opinion.

Further studies and discussions on the inappropriate use of corticosteroids to treat eye disorders are listed below.[2-10]

1. St Clair Roberts D. Steroids, the eye, and general practitioners. *BMJ* 1986; 292: 1414–15.
2. Lavin MJ, Rose GE. Use of steroid eye drops in general practice. *BMJ* 1986; 292: 1448–50.
3. Claoué CMP, Stevenson KE. Incidence of inappropriate treatment of herpes simplex keratitis with topical steroids. *BMJ* 1986; 292: 1450–1.
4. Livingstone A. Steroids, the eye, and general practitioners. *BMJ* 1986; 292: 1737.
5. Lawrence M. Steroids, the eye, and general practitioners. *BMJ* 1986; 292: 1737–8.
6. Trevor-Roper P. Steroids, the eye, and general practitioners. *BMJ* 1986; 292: 1738.
7. Jay B. Steroids, the eye, and general practitioners. *BMJ* 1986; 293: 205.
8. Rose GE, Lavin MJ. Steroids, the eye, and general practitioners. *BMJ* 1986; 293: 205.
9. O'Day DM. Corticosteroids: an unresolved debate. *Ophthalmology* 1991; 98: 845–6.
10. Stern GA, Buttross M. Use of corticosteroids in combination with antimicrobial drugs in the treatment of infectious corneal disease. *Ophthalmology* 1991; 98: 847–53.

Intranasal administration. Local adverse effects from intranasal corticosteroids include irritation, epistaxis, and smell and taste disturbances (see also p. 1615.3). Ulceration, septal perforation, and hypersensitivity reactions have occurred.[1]

There have been cases of Cushing's syndrome associated with inappropriately prolonged use of corticosteroid nasal drops in children.[2,3] Such drops should not be prescribed on a repeat prescription basis; where treatment is contemplated for more than 6 weeks appropriate monitoring has been recommended. See also Adrenal Suppression, under Adverse Effects, p. 1616.1.

1. Salib RJ, Howarth PH. Safety and tolerability profiles of intranasal antihistamines and intranasal corticosteroids in the treatment of allergic rhinitis. *Drug Safety* 2003; 26: 863–93.
2. Findlay CA, *et al.* Childhood Cushing's syndrome induced by betamethasone nose drops and repeat prescriptions. *BMJ* 1998; 317: 739–40.
3. Perry RJ, *et al.* Cushing's syndrome, growth impairment, and occult adrenal suppression associated with intranasal steroids. *Arch Dis Child* 2002; 87: 45–8.

Porphyria. Corticosteroids have generally been considered to be safe in patients with porphyria although there is conflicting evidence of porphyrinogenicity. In a review[1] of drug-induced porphyrias it was noted that a report suggesting that corticosteroids may have a role in treating the acute attack together with many reports attesting to their safety, contrasted with their repeated incrimination as the offending agent in producing such episodes. It was considered that as corticosteroids may be life-saving, they should be used if really indicated.

For classification of porphyrinogenicity by The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, of specific drugs, see under the individual monographs.

1. Moore MR, Disler PB. Drug-induction of the acute porphyrias. *Adverse Drug React Acute Poisoning Rev* 1983; 2: 149–89.

Pregnancy. Studies have shown that corticosteroid use in pregnant women did not have adverse effects on the fetus in terms of psychological development[1] or growth and general health factors.[2] However, in an isolated report[3] the topical use of triamcinolone in a pregnant woman for treatment of eczema was considered to have caused fetal growth retardation. In another study[4] of 11 women with placenta praevia given intramuscular betamethasone 12 mg repeated 24 hours later, there were 2 cases of constriction of the ductus arteriosus; neither case was severe.

Early studies in *animals* showed an increase in fetal cleft palate after maternal ingestion of high corticosteroid doses, and cortisone has been used widely as a tool for the investigation of mechanisms responsible for cleft lip and palate. With doses used in clinical practice, however, the risk appears to be low. In an analysis of several hundred cases reported in the literature[5] it was concluded that the incidence of cleft palate in exposed children was slightly higher than in a random sample, but that in the small selected group studied, this higher incidence might be fallacious. Although an increased incidence of malformations in the children of asthmatic mothers given prednisolone 2.5 to 30 mg daily during pregnancy was noted,[6] others[7] have suggested that the outcome might have been worse in untreated asthmatic mothers. Moreover, no significant increase in the risk of fetal or maternal complications was found in a study of asthmatic mothers given prednisolone 2.5 to 20 mg daily.[8] Subsequently, no evidence of a teratogenic effect for corticosteroids was noted in a comparison of the maternal drug histories of the mothers of 764 infants born with anomalies of the CNS and 764 controls,[9] and in another study[10] there were no striking differences in birth-weight and frequency of 'small for dates' infants born to mothers who received systemic corticosteroids during pregnancy for pemphigoid gestationis and those who did not.

Fears concerning the use of corticosteroids during late pregnancy relate to their direct adverse effects on the fetus. These involve the known adverse effects of corticosteroids, such as increased risk of infection and adrenal insufficiency. No such adverse effects were noted in the infants of 70 exposed pregnancies,[8] although there have been individual reports.[11,12] The potential dangers of maternal diabetogenic effects have been shown in a study of metabolic changes induced in diabetic women by salbutamol (used in the prevention of premature labour) which could be exacerbated by use of dexamethasone (to promote maturation of the fetal lung) with consequent danger to the fetus.[13]

A review[14] by the UK CSM concluded that there was no convincing evidence that corticosteroids caused an increased incidence of congenital abnormality. Prolonged or repeated use during pregnancy did increase the risk of intra-uterine growth retardation but this did not seem to be a problem following short-term treatment. It was noted that the ability of different corticosteroids to cross the placenta varied very markedly.

1. Schmand B, *et al.* Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. *Pediatrics* 1990; 86: 58–64.
2. Doyle LW, *et al.* Antenatal steroid therapy and 5-year outcome of extremely low birth weight infants. *Obstet Gynecol* 1989; 73: 743–6.
3. Katz VL, *et al.* Severe symmetric intrauterine growth retardation associated with the topical use of triamcinolone. *Am J Obstet Gynecol* 1990; 162: 396–7.
4. Wasserstrum N, *et al.* Betamethasone and the human fetal ductus arteriosus. *Obstet Gynecol* 1989; 74: 897–900.
5. Popert AJ. Pregnancy and adrenocortical hormones: some aspects of their interaction in rheumatic diseases. *BMJ* 1962; 1: 967–72.
6. Warrell DW, Taylor R. Outcome for the foetus of mothers receiving prednisolone during pregnancy. *Lancet* 1968; i: 117–18.
7. Scott JK. Foetal risk with maternal prednisolone. *Lancet* 1968; i: 208.
8. Schatz M, *et al.* Corticosteroid therapy for the pregnant asthmatic patient. *JAMA* 1975; 233: 804–7.
9. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; 59: 1052–60.
10. Holmes RC, Black MM. The fetal prognosis in pemphigoid gestationis (herpes gestationis). *Br J Dermatol* 1984; 110: 67–72.
11. Grajwer LA, *et al.* Neonatal subclinical adrenal insufficiency: result of maternal steroid therapy. *JAMA* 1977; 238: 1279–80.
12. Evans TJ, *et al.* Congenital cytomegalovirus infection after maternal renal transplantation. *Lancet* 1975; i: 1359–60.
13. Gündoğdu AS, *et al.* Comparison of hormonal and metabolic effects of salbutamol infusion in normal subjects and insulin-requiring diabetics. *Lancet* 1979; ii: 1317–21.
14. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; 24: 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE6dDocName=CON2023392&RevisionSelectionMethod=LatestReleased (accessed 16/06/06)

Septic shock. Some manufacturers recommend that corticosteroids should not be given to patients with septic shock and references to the controversial use of high-dose corticosteroids are given under Septic Shock, in Uses and Administration, p. 1613.1.

Sickle-cell disease. Sickle-cell crisis was reported to have been precipitated by corticosteroids in 2 patients with sickle C disease.[1] The crises in these patients were considered to have started with ischaemic necrosis of the bone marrow leading to fat embolism, cerebral hypoxia, and coma.

For mention of the use of corticosteroids in sickle-cell crisis, see under Sickle-cell Disease, in Uses and Administration, p. 1613.1.

1. Huang JC, *et al.* Sickling crisis, fat embolism, and coma after steroids. *Lancet* 1994; 344: 951–2.

Tooth erosion. The increased incidence of tooth erosion seen in patients with asthma might be related to the pH of inhaled powder (but not aerosol) formulations.[1] Beclomethasone dipropionate and fluticasone had pHs of 4.76 as powder formulations, whereas the pHs of the aerosols were well above the pH of 5.5 at which tooth substance begins to dissolve. Budesonide was less acidic in its powder formulation (pH 6.47).

1. O'Sullivan EA, Curzon MEJ. Drug treatments for asthma may cause erosive tooth damage. *BMJ* 1998; 317: 820.

Varicella. Several cases of fatal or near fatal chickenpox have been reported in patients receiving corticosteroids.[1-3] Although mostly associated with systemic use, severe disseminated varicella and staphylococcal pericarditis have been reported in an infant following a single application of a potent topical corticosteroid cream.[4] Guidelines issued by the UK CSM state that all patients taking systemic corticosteroids for purposes other than replacement, and who have not had chickenpox, should be regarded as being at risk of severe chickenpox, irrespective of the dose or duration of treatment.[2,5] Passive immunisation with varicella-zoster immunoglobulin should be given to non-immune patients who are receiving corticosteroids, or who have received them within the last 3 months, if they are exposed to chickenpox. Passive immunisation should preferably be given within 3 days and not later than 10 days from exposure.[2] The CSM considered that there was no good evidence that topical, inhaled, or rectal corticosteroids were associated with an increased risk of severe chickenpox.

1. Rice P, *et al.* Near fatal chickenpox during prednisolone treatment. *BMJ* 1994; 309: 1069–70.
2. CSM/MCA. Severe chickenpox associated with systemic corticosteroids. *Current Problems* 1994; 20: 1–2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_F_LE6dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 19/03/10)
3. Dowell SF, Breese JS. Severe varicella associated with steroid use. *Pediatrics* 1993; 92: 223–8.
4. Brumund MR, *et al.* Disseminated varicella and staphylococcal pericarditis after topical steroids. *J Pediatr* 1997; 131: 162–3.
5. Ellender D, *et al.* Severe chickenpox during treatment with corticosteroids. *BMJ* 1995; 310: 327.

Interactions of Corticosteroids

Concurrent use of barbiturates, carbamazepine, phenytoin, primidone, or rifampicin may enhance the metabolism and reduce the effects of systemic corticosteroids. Conversely oral contraceptives or ritonavir may increase plasma concentrations of corticosteroids. Use of corticosteroids with potassium-depleting diuretics, such as thiazides or furosemide, may cause excessive potassium loss. There is also an increased risk of hypokalaemia with concurrent amphotericin B or bronchodilator therapy with xanthines or beta$_2$ agonists. There may be an increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs. Response to anticoagulants may be altered by corticosteroids and requirements of antidiabetic drugs and antihypertensives may be increased. Corticosteroids may decrease serum concentrations of salicylates and may decrease the effect of anticholinesterases in myasthenia gravis. The antiglucocorticoid effect of mifepristone will antagonise the effects of corticosteroids.

Analgesics. For the effect of corticosteroids on *salicylates*, see Aspirin, Interactions, p. 26.3.

Antibacterials. *Rifampicin* reduces the activity of corticosteroids[1-6] by accelerating their metabolism, and a similar effect would be expected with other rifamycins. There is limited evidence that the macrolide antibacterials *troleandomycin*,[9-11] and perhaps *erythromycin*,[12] may inhibit the metabolism of methylprednisolone, but not of prednisolone.[10] Dosage reduction should be made as necessary if troleandomycin and methylprednisolone are used together. There is no evidence of a clinically significant interaction between these macrolides and other corticosteroids.

For reference to corticosteroids lowering plasma concentrations of *isoniazid* and enhancing its renal clearance, see p. 313.2.

1. Edwards OM, *et al.* Changes in cortisol metabolism following rifampicin therapy. *Lancet* 1974; ii: 549–51.
2. Maisey DN, *et al.* Rifampicin and cortisone replacement therapy. *Lancet* 1974; ii: 896–7.
3. Steenbergen GJ, Pfaltzgraff RE. Treatment of neuritis in borderline leprosy with rifampicin and corticosteroids—a pilot trial. *Lepr Rev* 1975; 46: 115–18.
4. Buffington GA, *et al.* Interaction of rifampin and glucocorticoids: adverse effect on renal allograft function. *JAMA* 1976; 236: 1958–60.
5. Hendrickse W, *et al.* Rifampicin-induced non-responsiveness to corticosteroid treatment in nephrotic syndrome. *BMJ* 1979; 1: 306.
6. van Marle W, *et al.* Concurrent steroid and rifampicin therapy. *BMJ* 1979; 1: 1020.
7. Jopline WH, Pettit JHS. Interaction between rifampicin, steroids and oral contraceptives. *Lepr Rev* 1979; 50: 331–2.
8. McAllister WAC, *et al.* Rifampicin reduces effectiveness and bioavailability of prednisolone. *BMJ* 1983; 286: 923–5.
9. Szefler SJ, *et al.* The effect of troleandomycin on methylprednisolone elimination. *J Allergy Clin Immunol* 1980; 66: 447–51.
10. Szefler SJ, *et al.* Steroid-specific and anticonvulsant interaction aspects of troleandomycin-steroid therapy. *J Allergy Clin Immunol* 1982; 69: 455–60.
11. Kamada AK, *et al.* Glucocorticoid reduction with troleandomycin in chronic severe asthmatic children: implication for future trials and clinical application. *J Allergy Clin Immunol* 1992; 89: 285.
12. LaForce CF, *et al.* Inhibition of methylprednisolone elimination in the presence of erythromycin therapy. *J Allergy Clin Immunol* 1983; 72: 34–9.

Anticoagulants. For the various effects of corticosteroids on anticoagulants, see under Warfarin Sodium, p. 1533.2.

Antiepileptics. Reduced efficacy of corticosteroids has been noted in asthmatic, arthritic, renal transplant, and other patients who also received *phenytoin* or *phenobarbital*,[1-3] and the clearance of corticosteroids has also been reported to be markedly increased by *carbamazepine*.[3] Hypoadrenalism occurred when *topiramate* was started in a patient who had been stabilised on corticosteroid replace-

ment therapy for congenital adrenal hyperplasia.[4] Induction of microsomal liver enzymes by the antiepileptic, resulting in enhanced metabolism of the corticosteroid is believed to be the underlying mechanism. Different corticosteroids appear to be affected to different degrees, but the disease state, doses, and other determinants such as diet, sex, and other drugs used may also be contributory factors. An increase in the dosage of the corticosteroids may be necessary in order to maintain the desired therapeutic response.[1]

1. Brooks SM, *et al.* Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *N Engl J Med* 1972; 286: 1125–8.
2. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; 18: 131–50.
3. Bartoszek M, *et al.* Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy. *Clin Pharmacol Ther* 1987; 42: 424–32.
4. Jacob K, Trainer PJ. Topiramate can induce hypoadrenalism in patients taking oral corticosteroid replacement. *BMJ* 2009; 338: 1076.

Antifungals. *Ketoconazole*[1,2] and *itraconazole*[3,4] increase serum-methylprednisolone concentrations and enhance methylprednisolone's adrenal suppressive effects. A 50% reduction in intravenous methylprednisolone dose was suggested during ketoconazole therapy.[2] A similar effect was not evident with oral prednisone[4,5] although some workers[6] found that ketoconazole reduced the total clearance of prednisolone given intravenously and of prednisone given orally. Itraconazole can also reduce the clearance of dexamethasone; in a study[7] of 8 healthy subjects, the area under the concentration-time curve (AUC) for both intravenous and oral dexamethasone was increased about 3.5-fold, and the morning plasma-cortisol concentration was suppressed for at least 2 days longer. A study[8] of healthy subjects found that ketoconazole increased the AUC for oral budesonide more than sixfold when they were given together, but only about fourfold when the doses were given 12 hours apart. Systemic exposure to inhaled budesonide is increased by itraconazole, which probably reduces the metabolism of budesonide.[9] Adrenal suppression was found in 11 of 25 patients with cystic fibrosis who were treated with this combination; one patient developed Cushing's syndrome.[10] A similar interaction may have been the cause of significant adrenal suppression in a patient with cystic fibrosis who was treated with itraconazole and inhaled fluticasone propionate.[11]

1. Glynn AM, *et al.* Effects of ketoconazole on methylprednisolone pharmacokinetics and cortisol secretion. *Clin Pharmacol Ther* 1986; 39: 654–9.
2. Kandrotas RJ, *et al.* Ketoconazole effects on methylprednisolone disposition and their joint suppression of endogenous cortisol. *Clin Pharmacol Ther* 1987; 42: 465–70.
3. Varis T, *et al.* Plasma concentrations and effects of oral methylprednisolone are considerably increased by itraconazole. *Clin Pharmacol Ther* 1998; 64: 363–8.
4. Lebrun-Vignes B, *et al.* Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. *Br J Clin Pharmacol* 2001; 51: 443–50.
5. Ludwig BA, *et al.* Steroid-specific effects of ketoconazole on corticosteroid disposition: unaltered prednisolone elimination. *DICP Ann Pharmacother* 1989; 23: 858–61.
6. Zürcher RM, *et al.* Impact of ketoconazole on the metabolism of prednisolone. *Clin Pharmacol Ther* 1989; 45: 366–72.
7. Varis T, *et al.* The cytochrome P450 3A4 inhibitor itraconazole markedly increases the plasma concentrations of dexamethasone and enhances its adrenal-suppressant effect. *Clin Pharmacol Ther* 2000; 68: 487–94.
8. Seidegård J. Reduction of the inhibitory effect of ketoconazole on budesonide pharmacokinetics by separation of their time of administration. *Clin Pharmacol Ther* 2000; 68: 13–17.
9. Raaska K, *et al.* Plasma concentrations of inhaled budesonide and its effects on plasma cortisol are increased by the cytochrome P4503A4 inhibitor itraconazole. *Clin Pharmacol Ther* 2002; 72: 362–9.
10. Skov M, *et al.* Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. *Eur Respir J* 2002; 20: 127–33.
11. Parmar JS, *et al.* Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. *Thorax* 2002; 57: 749–50.

Antineoplastics. For reference to single doses of prednisone inhibiting the activation of *cyclophosphamide* (but longer-term treatment increasing its activation), see Cyclophosphamide, p. 773.3.

Antivirals. For a possible effect of corticosteroids on the metabolism of HIV-protease inhibitors, see p. 988.1.

Ritonavir can greatly increase plasma concentrations of fluticasone, through inhibition of cytochrome P450 isoenzyme CYP3A4, leading to systemic corticosteroid effects including Cushing's syndrome and adrenal suppression.[1-3] There have been reports of osteoporosis, with fractures in one case, associated with Cushing's syndrome due to this interaction.[2] Similar interactions are expected with other HIV-protease inhibitors.

1. GlaxoSmithKline, Canada. Important safety information regarding a drug interaction between fluticasone propionate (Flonase/Flovent/Advair) and ritonavir (Norvir/Kaletra), issued 22 January, 2004. Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/fluticasone_ritonavir_hpc-cps-eng.pdf (accessed 22/08/08)
2. Samaras K, *et al.* Iatrogenic Cushing's syndrome with osteoporosis and secondary adrenal failure in human immunodeficiency virus-infected patients receiving inhaled corticosteroids and ritonavir-boosted protease inhibitors: six cases. *J Clin Endocrinol Metab* 2005; 90: 4394–8.
3. Johnson SR, *et al.* Cushing syndrome with secondary adrenal insufficiency from concomitant therapy with ritonavir and fluticasone. *J Pediatr* 2006; 148: 386–8.

Calcium-channel blockers. Studies in healthy subjects have found that *diltiazem* reduces the clearance of methylprednisolone.[1,2]

1. Varis T, *et al.* Diltiazem and mibefradil increase the plasma concentrations and greatly enhance the adrenal-suppressant effect of oral methylprednisolone. *Clin Pharmacol Ther* 2000; 67: 215–21.
2. Booker BM, *et al.* Pharmacokinetic and pharmacodynamic interactions between diltiazem and methylprednisolone in healthy volunteers. *Clin Pharmacol Ther* 2002; 72: 370–82.

Gastrointestinal drugs. *Aprepitant* increased plasma concentrations of dexamethasone and methylprednisolone in a pharmacokinetic study.[1] Licensed product information for aprepitant recommends that the usual dose of oral dexamethasone be reduced by 50%, and the dose of methylprednisolone by about 25% when given intravenously, and by 50% when given orally. For the appropriate regimen when these drugs are given together for nausea and vomiting, see Administration under Aprepitant, p. 1819.3.

1. McCrea JB, *et al.* Effects of the neurokinin$_1$ receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. *Clin Pharmacol Ther* 2003; 74: 17–24.

Growth hormone. Somatropin (growth hormone) therapy may impair the conversion of cortisone and prednisone to their active metabolites, cortisol and prednisolone, respectively. This occurs through the inhibition of the microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 in hepatic and adipose tissues. Licensed product information suggests that patients should be monitored for the need to increase doses of cortisone or prednisone after somatropin is started. Studies of cortisone acetate in hypopituitary patients receiving growth hormone replacement have reached different conclusions; some concluded that the effect may be insignificant,[1] while others suggested that dose adjustments may be needed.[2,3]

Somatropin may increase the clearance of corticosteroids that are metabolised by the cytochrome P450 isoenzyme CYP3A4, although the clinical significance of this is unknown.

High doses of corticosteroids may inhibit the growth promoting effects of somatropin.

1. Beentjes JAM, *et al.* Effects of growth hormone replacement on cortisol metabolism in hypopituitary patients treated with cortisone acetate. *Scand J Clin Lab Invest* 2001; 61: 277–86.
2. Swords FM, *et al.* The effects of growth hormone deficiency and replacement on glucocorticoid exposure in hypopituitary patients on cortisone acetate and hydrocortisone replacement. *Clin Endocrinol (Oxf)* 2003; 59: 613–20.
3. Sigurjonsdottir HA, *et al.* Lack of regulation of 11 β -hydroxysteroid dehydrogenase type 1 during short-term manipulation of GH in patients with hypopituitarism. *Eur J Endocrinol* 2009; 161: 375–80.

Histamine. For the effect of systemic corticosteroids on histamine given exogenously, see p. 2525.3.

Immunosuppressants. It has been suggested that mutual inhibition of metabolism occurs between *ciclosporin* and corticosteroids, and may increase the plasma concentrations of either drug.[1,2] A review[3] cited studies supporting this conclusion but also mentioned studies that showed that ciclosporin did not significantly decrease clearance of prednisolone[4] and that corticosteroids either did not change, or decreased, ciclosporin concentrations.[5,6] Some of these conflicting results may be due to differences in the methods used to measure ciclosporin concentrations.

1. Ost L. Effects of cyclosporin on prednisolone metabolism. *Lancet* 1984; i: 451.
2. Klintmalm G, Säwe J. High dose methylprednisolone increases plasma cyclosporin levels in renal transplant recipients. *Lancet* 1984; i: 731.
3. Yee GC, McGuire TR. Pharmacokinetic drug interactions with cyclosporin (part II). *Clin Pharmacokinet* 1990; 19: 400–15.
4. Frey FJ, *et al.* Evidence that cyclosporine does not affect the metabolism of prednisolone after renal transplantation. *Transplantation* 1987; 43: 494–8.
5. Ptachcinski RJ, *et al.* Cyclosporine - high-dose steroid interaction in renal transplant recipients: assessment by HPLC. *Transplant Proc* 1987; 19: 1728–9.
6. Hricik DE, *et al.* Association of the absence of steroid therapy with increased cyclosporine blood levels in renal transplant recipients. *Transplantation* 1990; 49: 221–3.

Leukotriene antagonists. Severe peripheral oedema occurred in a patient treated with *montelukast* and prednisone for asthma, but not when either drug was used alone.[1] Montelukast may have potentiated sodium and fluid retention caused by the corticosteroid.

1. Geller M. Marked peripheral edema associated with montelukast and prednisone. *Ann Intern Med* 2000; 132: 924.

Lipid regulating drugs. Giving *colestipol* to a patient with hypopituitarism taking oral hydrocortisone maintenance therapy resulted in headaches, ataxia, and lethargy.[1] Mental status returned to normal within hours of an intravenous dose of hydrocortisone 100 mg, and colestipol was subsequently withdrawn uneventfully.

1. Nekl KE, Aron DC. Hydrocortisone-colestipol interaction. *Ann Pharmacother* 1993; 27: 980–1.

Neuromuscular blockers. For reference to corticosteroids antagonising the effects of *competitive neuromuscular blockers*, see under Atracurium, p. 2032.3.

Sex hormones. There have been reviews[1,2] discussing several reports of an enhanced effect of corticosteroids in women also receiving *oestrogens* or *oral contraceptives* and commenting that the dose of corticosteroids in some cases may need to be reduced. There is some evidence that budesonide may be less affected by use with oral contraceptives than prednisolone.[3]

1. Shenfield GM. Drug interactions with oral contraceptive preparations. *Med J Aust* 1986; 144: 205–10.
2. Back DJ, Orme ML'E. Pharmacokinetic drug interactions with oral contraceptives. *Clin Pharmacokinet* 1990; 18: 472–84.
3. Seidegård J, *et al.* Effect of an oral contraceptive on the plasma levels of budesonide and prednisolone and the influence on plasma cortisol. *Clin Pharmacol Ther* 2000; 67: 373–81.

Smoking. There was a report of an appreciable and consistent increase in plasma corticosteroids after cigarette smoking.[1] However, a review concerning the clinical importance of smoking and drug interactions[2] concluded that in the majority of examples, including corticosteroids, there was little evidence of a recognisable hazard from the interaction.

1. Kershbaum A, *et al.* Effect of smoking and nicotine on adrenocortical secretion. *JAMA* 1968; 203: 275–8.
2. D'Arcy PF. Tobacco smoking and drugs: a clinically important interaction? *Drug Intell Clin Pharm* 1984; 18: 302–7.

Sympathomimetics. Studies in 21 asthmatic patients suggested that the plasma half-life of dexamethasone was decreased by *ephedrine*.[1] More importantly use of corticosteroids with *beta$_2$ agonists* may potentiate any hypokalaemic effects.[2]

1. Brooks SM, *et al.* The effects of ephedrine and theophylline on dexamethasone metabolism in bronchial asthma. *J Clin Pharmacol* 1977; 17: 308–18.
2. CSM. β_2 agonists, xanthines and hypokalaemia. *Current Problems* 24, 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 23/03/10)

Thalidomide. In a double-blind crossover study of thalidomide in the treatment of severe chronic erythema nodosum leprosum,[1] the dose of prednisolone necessary to suppress symptoms was considerably reduced in 9 of 10 patients while they were receiving thalidomide; there has been a comment[2] that prednisolone should not be given with thalidomide.

For reference to a possible interaction between thalidomide and dexamethasone, see Effects on the Skin under Adverse Effects of Thalidomide, p. 870.2.

1. Waters MFR. An internally-controlled double blind trial of thalidomide in severe erythema nodosum leprosum. *Lepr Rev* 1971; 42: 26–42.
2. WHO. Regional Office for the Western Pacific. Final report on the first regional working group on leprosy, Manila, Philippines, 7–12 December 1978. *Lepr Rev* 1979; 50: 326–9.

Xanthines. For the effect of corticosteroids on *aminophylline* and *theophylline*, see p. 1235.3.

Pharmacokinetics of Corticosteroids

Corticosteroids are, in general, readily absorbed from the gastrointestinal tract. They are also absorbed when given locally. After topical use, particularly under an occlusive dressing or when the skin is broken, or use rectally as an enema, sufficient corticosteroid may be absorbed to give systemic effects; this is also a possibility with other local routes such as inhalation. Water-soluble forms of corticosteroids are given by intravenous injection for rapid response; more prolonged effects are achieved using lipid-soluble forms of corticosteroids by intramuscular injection.

Corticosteroids are rapidly distributed to all body tissues. They cross the placenta to varying degrees and may be distributed in small amounts into breast milk.

Most corticosteroids in the circulation are extensively bound to plasma proteins, mainly to globulin and less so to albumin. The corticosteroid-binding globulin (transcortin) has high affinity but low binding capacity, while albumin has low affinity but large binding capacity. The synthetic corticosteroids are less extensively protein bound than hydrocortisone (cortisol). They also tend to have longer half-lives.

Corticosteroids are metabolised mainly in the liver but also in other tissues, and are excreted in the urine. The slower metabolism of the synthetic corticosteroids with their lower protein-binding affinity may account for their increased potency compared with the natural corticosteroids.

Reviews.

1. Begg EJ, *et al.* The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; 146: 37–41.
2. McGhee CNJ. Pharmacokinetics of ophthalmic corticosteroids. *Br J Ophthalmol* 1992; 76: 681–4.
3. Jusko WJ. Pharmacokinetics and receptor-mediated pharmacodynamics of corticosteroids. *Toxicology* 1995; 102: 189–96.
4. Derendorf H, *et al.* Pharmacokinetics and pharmacodynamics of inhaled corticosteroids. *J Allergy Clin Immunol* 1998; 101 (suppl 2): S440–6.
5. Czock D, *et al.* Pharmacokinetics and pharmacodynamics of systemical / administered glucocorticoids. *Clin Pharmacokinet* 2005; 44: 61–98.

Alclometasone Dipropionate

(BANM, USAN, rINNM) ⊗

Alclometasona, dipropionato de; Alclométasone, Dipropionate d'; Alclometasoni Dipropionas; Alklometasondipropionaat; Alklometasonidipropionaatti; Dipropionato de alclometasona; Sch-22219; Альклометазона Дипропионат.

7α-Chloro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

$C_{28}H_{37}ClO_7$=521.0

CAS — 67452-97-5 (alclometasone); 66734-13-2 (alclometasone dipropionate).

ATC — D07AB10; S01BA10.

ATC Vet — QD07AB10; QS01BA10.

UNII — S56PQL4N1V.

Pharmacopoeias. In *US.*

USP 36: (Alclometasone Dipropionate). Store in airtight containers.

Profile

Alclometasone dipropionate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see Topical Application, p. 1599.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies alclometasone as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Afloderm; *Ger.*: Delonal†; *Gr.*: Lomesone; *Hong Kong*: Perderm†; *Indon.*: Cloderm; Perderm; *Irl.*: Modrasone; *Ital.*: Legederm; *Mex.*: Logoderm†; *Pol.*: Afloderm; *Port.*: Miloderme; *Rus.*: Afloderm (Афлодерм); *UK*: Modrasone; *USA*: Adovate; *Venez.*: Demiderm.

Pharmacopoeial Preparations

USP 36: Alclometasone Dipropionate Cream; Alclometasone Dipropionate Ointment.

Aldosterone *(BAN, rINN)*

Aldosteron; Aldosterona; Aldostérone; Aldosteroni; Aldosteronum; Electrocortin; Альдостерон.

11β,18-Epoxy-18,21-dihydroxypregn-4-ene-3,20-dione.

$C_{21}H_{28}O_5$=360.4

CAS — 52-39-1.

ATC — H02AA01.

ATC Vet — QH02AA01.

UNII — 4964P6T9RB.

Uses and Administration

Aldosterone is the main mineralocorticoid (p. 1597.1) secreted by the adrenal cortex. It has no significant glucocorticoid (anti-inflammatory) properties.

Aldosterone has been given by intramuscular or intravenous injection, with a glucocorticoid, in the treatment of primary adrenocortical insufficiency (p. 1600.2) but synthetic mineralocorticoids such as fludrocortisone (p. 1634.3), which can be given orally, are usually preferred. It has also been used as the sodium succinate.

Adverse Effects

Aldosterone has very pronounced mineralocorticoid actions and little effect on carbohydrate metabolism. It may therefore have the mineralocorticoid adverse effects described for the corticosteroids in general (p. 1615.3).

Amcinonide *(BAN, USAN, rINN)* ⊗

Amcinonida; Amcinonidum; Amcinopol; CL-34699; Амцинонид.

16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{28}H_{35}FO_7$=502.6

CAS — 51022-69-6.

ATC — D07AC11.

ATC Vet — QD07AC11.

UNII — 423W026MA9.

Pharmacopoeias. In *US.*

Profile

Amcinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Amicla; *Canad.*: Cyclocort; *Fr.*: Penticort†; *Ger.*: Amcidem; *Mex.*: Visderm H; *Thai.*: Amciderm†; Visderm.

Pharmacopoeial Preparations

USP 36: Amcinonide Cream; Amcinonide Ointment.

Beclometasone Dipropionate

(BANM, rINNM) ⊗

Beclometasona, dipropionato de; Béclométasone, dipropionate de; Beclometasoni dipropionas; Beclometasoni Dipropionas; Beclomethasone Dipropionate (USAN); Beclomethasone Dipropionate; Beklometasondipropionat; Beklometason-dipropionát; Beklometasonidipropionaatti; Beklométazon Dipropiyonat; Beklometazon-dipropionát; Beklometazono dipropionatas; Beklometazonu dipropionian; 9α-Chloro-16β-methylprednisolone Dipropionate; Dipropionato de beclometasona; Sch-18020W; Беклометазона Дипропионат.

9α-Chloro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate.

$C_{28}H_{37}ClO_7$=521.0

CAS — 4419-39-0 (beclometasone); 5534-09-8 (beclometasone dipropionate).

ATC — A07EA07; D07AC15; R01AD01; R03BA01.

ATC Vet — QA07EA07; QD07AC15; QR01AD01; QR03BA01.

UNII — 5B307S63B2 (beclomethasone dipropionate); 4H7L9AI22I (beclomethasone dipropionate monohydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.*

US allows either the anhydrous or monohydrate form. *Eur.* also includes a separate monograph for the monohydrate.

Ph. Eur. 8: (Beclometasone Dipropionate, Anhydrous). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

Ph. Eur. 8: (Beclometasone Dipropionate Monohydrate). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 36: (Beclomethasone Dipropionate). It is anhydrous or contains one molecule of water of hydration. A white to cream white, odourless powder. Very slightly soluble in water; freely soluble in alcohol and in acetone; very soluble in chloroform.

Uses and Administration

Beclometasone dipropionate is a corticosteroid with mainly glucocorticoid activity (p. 1597.1).

It is stated to exert a topical effect on the lungs without significant systemic activity at recommended doses (but see Adrenal Suppression under Adverse Effects, p. 1622.2), and is used by inhalation for the prophylaxis of **asthma** (see below). Many formulations are now available, with differing dosage regimens, and the appropriate product literature should be consulted before starting therapy or changing to another formulation. Furthermore, in the UK the doses of beclometasone dipropionate for asthma are expressed in terms of the amount supplied into the mouthpiece per actuation, whereas in the USA doses are expressed in terms of the amount emitted from the mouthpiece; recommended doses therefore appear somewhat lower in the USA than the UK doses given below, although in practical terms there is probably no difference.

In the UK the initial dose of most aerosol and dry powder inhalers is generally 200 to 400 micrograms daily for mild asthma, and 600 to 1600 micrograms daily for moderate to severe asthma. The dose should be adjusted according to response, and reduced to the lowest effective dose for maintenance. The usual maintenance dose is in the region of 400 to 800 micrograms daily, but up to 2 mg daily may be necessary in severe asthma. Therapy is usually given in 2 divided doses, although high-dose therapy may be given in 4 divided doses. Owing to differences in the relative bioavailability to the lungs, some powder inhalation delivery systems may be licensed for higher initial doses, although maximum doses are similar to those above. In contrast, some hydrofluoroalkane (CFC-free) inhalers must be used in lower doses: typical UK doses for one product (*Qvar; Ivax, UK*) range from 100 to 200 micrograms daily in mild asthma to 400 to 800 micrograms daily in severe asthma, given as 2 divided doses. See also Reformulation, p. 1622.3.

Beclometasone dipropionate is also used as a nasal spray and, like inhalation formulations used for asthma (see above), doses may appear to vary between countries depending on whether the dose is expressed in terms of the amount of drug supplied into, or emitted from, the nasal adaptor per actuation. In the prophylaxis and treatment of allergic and non-allergic **rhinitis** (p. 612.1), usual doses are 100 micrograms in each nostril twice daily or 50 micrograms in each nostril 3 or 4 times daily; a total of 400 micrograms daily should not generally be exceeded. A dose of 50 micrograms in each nostril twice daily may be sufficient for prophylaxis. The nasal spray is also used to prevent recurrence of **nasal polyps** after surgical removal (p. 1608.2).

Locally-acting formulations of beclometasone dipropionate are used in the management of **inflammatory bowel disease** (see p. 1622.1). In mild to moderate ulcerative colitis, a modified-release oral tablet is given in a dose of 5 mg once daily in the morning, before or after breakfast. Ulcerative colitis affecting the distal colon or rectum may be treated locally with a retention enema, usually in a dose of 3 mg daily at bedtime, or 1 mg once or twice daily. Treatment is usually given for 3 to 4 weeks.

Beclometasone dipropionate is also used topically in the treatment of various **skin disorders**. It is generally applied as a cream or ointment containing 0.025%. Beclometasone salicylate has also been used topically. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, see below.

Administration in children. Beclometasone dipropionate, given by inhalation, is used in children in the prophylaxis of **asthma**. The appropriate product information should be consulted before starting therapy or changing to another formulation because of the range of products available and the different ways in which doses may be expressed (see Uses, above). In the UK the dose of most aerosol and dry powder inhalers for children aged 6 years and older is generally 100 micrograms given 2 to 4 times daily. The dose should be adjusted according to response, and reduced to the lowest effective dose for maintenance. In the USA, a hydrofluoroalkane (CFC-free) inhaler (*Qvar; Ivax, USA*), is licensed for use in children aged 5 years and older. Expressed in terms of the amount of drug delivered from the mouthpiece, the initial dose is 40 micrograms twice daily, which is then adjusted according to response; the recommended maximum dose is 80 micrograms twice daily.

In the treatment and prophylaxis of **rhinitis**, children over 6 years of age may be given adult doses (see above).

Adenoidal hypertrophy. Although normally managed by surgery (or if less severe simply by symptomatic relief) adenoidal hypertrophy in children was reported to respond to aqueous nasal beclometasone 336 micrograms daily in an 8-week crossover study.[1] Improvements in adenoidal obstruction and symptom scores were enhanced in a subsequent 16-week follow-on study using 168 micrograms daily. Another similar study,[2] of an initial 4-week crossover period followed by 24 weeks of open-label treatment, found symptomatic improvements in about half of the patients, and at 100 weeks there was a decrease in the rate of adenotonsillectomy in children who had responded to beclometasone compared with nonresponders.

1. Demain JG, Goetz DW. Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. *Pediatrics* 1995; 95: 355–64.
2. Criscuoli G, *et al.* Frequency of surgery among children who have adenotonsillar hypertrophy and improve after treatment with nasal beclomethasone. Abstract: *Pediatrics* 2003; 111: 663. Full version: http://pediatrics.aappublications.org/cgi/content/full/111/3/e236 (accessed 27/04/04)

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

High-dose regimens may pose problems of compliance if beclometasone must be inhaled several times daily.

However, one study[1] found once-daily inhalation to be as effective as the same dose divided into 2 daily inhalations in short-term control of moderate asthma. Also there have been doubts that increasing the dose of inhaled beclometasone brings about increased benefits,[2] but guidelines and clinical practice suggest that improved control can often be achieved by increasing the dose. A systematic review[3] noted that while there was little evidence of an effect of dose titration above 400 micrograms daily in those with mild to moderate asthma, evidence was lacking in patients with more severe disease (who are more likely to be given high-dose therapy), and studies were needed to resolve the question.

Inhalation of beclometasone dipropionate as a nebulised solution has been found to be useful in the management of severe asthma in children aged 2 years or under previously unresponsive to other drugs.[4] Nebulised beclometasone dipropionate was also effective in the management of recurrent episodes of bronchopulmonary obstruction after bronchiolitis in children under 2 years of age.[5] However, in other reports nebulised beclometasone dipropionate, although more effective than saline in pre-school children, produced a response less than that usually seen with inhalation of beclometasone from an aerosol or capsules,[6] or no benefit at all.[7] This may have been due to beclometasone somehow failing to reach the lungs.[8] In pre-school children able to use a spacer device with a metered aerosol, intermittent therapy with high-dose beclometasone dipropionate, given at the first sign of symptoms, reduced the severity of acute episodic asthma.[9]

1. Gagnon M, *et al.* Comparative safety and efficacy of single or twice daily administration of inhaled beclomethasone in moderate asthma. *Chest* 1994; **105**: 1732–7.
2. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal axis. *Eur Respir J* 1994; **7**: 2179–84.
3. Adams NP, *et al.* Beclomethasone versus placebo for chronic asthma. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2005 (accessed 22/08/08).
4. Pedersen W, Prahl P. Jet-nebulized beclomethasone dipropionate in the management of bronchial asthma: topical steroids for asthmatic children younger than 4 years. *Allergy* 1987; **42**: 272–5.
5. Carlsen KH, *et al.* Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch Dis Child* 1988; **63**: 1428–33.
6. Storr J, *et al.* Nebulised beclomethasone dipropionate in preschool asthma. *Arch Dis Child* 1986; **61**: 270–3.
7. Webb MSC, *et al.* Nebulised beclomethasone dipropionate suspension. *Arch Dis Child* 1986; **61**: 1108–10.
8. Clarke SW. Nebulised beclomethasone dipropionate suspension: commentary. *Arch Dis Child* 1986; **61**: 1110.
9. Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child* 1990; **65**: 407–10.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

Cough. In children with recurrent cough inhalation of beclometasone 200 micrograms twice daily from a conventional aerosol or salbutamol 200 micrograms twice daily had no effect on cough frequency or severity.[1] However, in another study of 200 adults, use of beclometasone, salbutamol, or sodium cromoglicate (all in aerosol formulation) given 15 minutes before anaesthesia, significantly decreased coughing caused by fentanyl when compared with placebo. Of the 50 patients given beclometasone, none experienced coughing.[2]

1. Chang AB, *et al.* A randomised, placebo controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch Dis Child* 1998; **79**: 6–11.
2. Agarwal A, *et al.* Salbutamol, beclomethasone or sodium chromoglycate suppress coughing induced by iv fentanyl. *Can J Anesth* 2003; **50**: 297–300.

Graft-versus-host disease. Beclometasone is under investigation for its topical effect in the treatment of intestinal graft-versus-host disease (GVHD) that can develop after haematopoietic stem cell transplantation (p. 1933.1). A few small studies have suggested that oral beclometasone dipropionate, given with an induction course of oral prednisone for systemic effect, can increase caloric intake, improve gastrointestinal symptoms, and provide an overall survival advantage in acute GVHD.[1] Promising results have also been reported in chronic intestinal GVHD.[2] Repeated courses may be needed in some patients to achieve and maintain response, but prolonged therapy appears to be feasible.[3]

1. Doan PL, Chao NJ. The role of oral beclometasone dipropionate in the treatment of gastrointestinal graft-versus-host disease. *Drugs* 2009; **69**: 1339–50.
2. Villanueva FN, *et al.* Oral beclomethasone dipropionate for the treatment of gastrointestinal chronic graft-versus-host disease. *Biol Blood Marrow Transplant* 2009; **15**: 1331–6.
3. Iyer RV, *et al.* Long-term use of oral beclomethasone dipropionate for the treatment of gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant* 2005; **11**: 587–92.

Inflammatory bowel disease. Beclometasone dipropionate 500 micrograms given nightly as an enema was as effective as betamethasone phosphate 5 mg enemas in the treatment of acute attacks of distal ulcerative colitis.[1] Although betamethasone produced slightly superior histological improvement and faster disappearance of blood from the stools, systemic adverse effects noted with betamethasone therapy were absent in patients treated with beclometasone.

Comparisons of beclometasone dipropionate enemas (3 mg) with prednisolone sodium phosphate enemas[2] (30 mg) or mesalazine enemas[3] (1 g) found them to be equally effective. Treatment was well tolerated. Beclometasone dipropionate has also been studied for the oral treatment of ulcerative colitis.[4,5]

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p. 1808.3.

1. Halpern Z, *et al.* A controlled trial of beclomethasone versus betamethasone enemas in distal ulcerative colitis. *J Clin Gastroenterol* 1991; **13**: 38–41.
2. Campieri M, *et al.* Beclomethasone dipropionate enemas versus prednisolone sodium phosphate enemas in the treatment of distal ulcerative colitis. *Aliment Pharmacol Ther* 1998; **12**: 361–6.
3. Glioncheti P, *et al.* Italian BDP Study Group. Topical treatment of distal active ulcerative colitis with beclomethasone dipropionate or mesalamine: a single-blind randomized controlled trial. *J Clin Gastroenterol* 2005; **39**: 291–7.
4. Rizzello F, *et al.* Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2002; **16**: 1109–16.
5. Campieri M, *et al.* Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003; **17**: 1471–80.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Adrenal suppression may occur in some patients treated with high-dose long-term inhalation therapy for asthma. It has been stated that in the majority of patients no significant suppression is likely to occur when total daily doses of less than 1.5 mg are used (but see Adrenal Suppression, below).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Systemic absorption may also follow nasal use, particularly after high doses or prolonged treatment.

Adrenal suppression. The problem of adrenal suppression with corticosteroids is discussed on p. 1616.1. Listed below are some references and correspondence concerning adrenal suppression due to beclometasone inhalation therapy,[1-8] in some cases occurring with doses below 1.5 mg daily.[6] However, one study found that function of the hypothalamic-pituitary-adrenal axis remained normal in most patients at beclometasone doses below 3 mg daily.[9]

1. Grant IWB, Crompton GK. Becloforte inhaler. *BMJ* 1983; **286**: 644–5.
2. Slessor IM. Becloforte inhaler. *BMJ* 1983; **286**: 645.
3. Ebden P, Davies BH. High-dose corticosteroid inhalers for asthma. *Lancet* 1984; **ii**: 576.
4. Law CM, *et al.* Nocturnal adrenal suppression in asthmatic children taking inhaled beclomethasone dipropionate. *Lancet* 1986; **i**: 942–4.
5. Brown HM. Nocturnal adrenal suppression in children inhaling beclomethasone dipropionate. *Lancet* 1986; **i**: 1269.
6. Maxwell DL, Webb J. Adverse effects of inhaled corticosteroids. *BMJ* 1989; **298**: 827–8.
7. Priftis K, *et al.* Adrenal function in asthma. *Arch Dis Child* 1990; **65**: 838–40.
8. Tabachnik E, Zadik Z. Diurnal cortisol secretion during therapy with inhaled beclomethasone dipropionate in children with asthma. *J Pediatr* 1991; **118**: 294–7.
9. Brown PH, *et al.* Large volume spacer devices and the influence of high dose beclomethasone dipropionate on hypothalamo-pituitary-adrenal axis function. *Thorax* 1993; **48**: 233–8.

Candidiasis. Results of a study involving 229 asthmatic children indicated that the presence of a sore throat or a hoarse voice was not related to the presence of *Candida* or to treatment with inhaled beclometasone.[1] The occurrence of only one clinical case of oral candidiasis in 129 of the children receiving beclometasone confirmed previous observations that it is an uncommon finding in children compared with the reported incidence of between 4.5 and 13% in adults. The incidence of colonisation with *Candida* was greater in those children who received corticosteroids than in those who did not but was not affected by either the dose or type of inhaler used.

1. Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986; **61**: 788–90.

Effects on the bones. The adverse effects of corticosteroids in general on bones are discussed on p. 1616.2.

Studies in healthy subjects have shown that inhaled beclometasone dipropionate can suppress bone metabolism.[1-3] These studies measured biochemical markers such as serum-osteocalcin concentrations, serum alkaline phosphatase activity, and urinary hydroxyproline-creatinine ratio, over short periods of time. Another study found that markers of collagen turnover, but not osteocalcin, were reduced by beclometasone or budesonide 800 micrograms daily in mildly asthmatic children.[4] Results are difficult to interpret since osteocalcin concentrations are reduced in patients with asthma regardless of treatment,[5] and it is uncertain whether significant bone loss does occur in practice. One 12-month study[6] in adults with asthma found that biochemical markers showed suppressed bone formation from inhaled beclometasone, and that there was some loss of bone mineral density from the hip. This study also found that inhaled fluticasone, in equivalent therapeutic doses, may have less adverse effect on bone. Another, smaller, study[7] found no adverse effects from beclometasone or fluticasone on bone mass or metabolism. In a study[8] of asthmatic children, comparing those treated with inhaled budesonide with those who received no corticosteroids, an average daily dose of about 500 micrograms budesonide for 3 to 6 years did not adversely affect bone density and mineral measures.

1. Pouw EM, *et al.* Beclomethasone inhalation decreases serum osteocalcin concentrations. *BMJ* 1991; **302**: 627–8.
2. Ali N, *et al.* Beclomethasone and osteocalcin. *BMJ* 1991; **302**: 1080.
3. Teelucksingh S, *et al.* Inhaled corticosteroids, bone formation and osteocalcin. *Lancet* 1991; **338**: 60–1.
4. Birkebæk NH, *et al.* Bone and collagen turnover during treatment with inhaled dry powder budesonide and beclomethasone dipropionate. *Arch Dis Child* 1995; **73**: 524–7.
5. König P, *et al.* Bone metabolism in children with asthma treated with inhaled beclomethasone dipropionate. *J Pediatr* 1993; **122**: 219–26.
6. Pauwels RA, *et al.* Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. *Am J Respir Crit Care Med* 1998; **157**: 827–32.
7. Medici TC, *et al.* Effect of one year treatment with inhaled fluticasone propionate or beclomethasone dipropionate on bone density and bone metabolism: a randomised parallel group study in adult asthmatic subjects. *Thorax* 2000; **55**: 375–82.
8. Agertoft L, Pedersen S. Bone mineral density in children with asthma receiving long-term treatment with inhaled budesonide. *Am J Respir Crit Care Med* 1998; **157**: 178–83.

Effects on growth. Meta-analysis of 3 eligible studies (out of 92 examined) concluded that inhaled beclometasone therapy at a dose of 400 micrograms daily may cause a 1.54 cm/year decrease in growth in children with mild to moderate asthma.[1] The long-term effects of treatment are unknown, and therefore it is not clear whether catch-up growth will occur on stopping therapy. The lowest possible dose of corticosteroid therapy should be used in asthma, and growth should be monitored.[1] There is also evidence[2] that long-term intranasal beclometasone for the treatment of allergic rhinitis can slow growth in children; the effect on final height is unknown. For further details of the effects of corticosteroids on growth, see p. 1617.2.

1. Sharek PJ, *et al.* Beclomethasone for asthma in children: effects on linear growth. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).
2. Skoner DP, *et al.* Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Abstract *Pediatrics* 2000; **105**: 415–16. Full version: http://pediatrics.aappublications.org/cgi/content/full/105/2/e23 (accessed 27/04/04)

Effects on the lungs. Pulmonary eosinophilia has occurred in patients treated with inhaled beclometasone.[1-4]

1. Paterson IC, *et al.* Pulmonary eosinophilia after substitution of aerosol for oral corticosteroid therapy. *Br J Dis Chest* 1975; **69**: 217–22.
2. Hudgel DW, Spector SL. Pulmonary infiltration with eosinophilia recurrence in an asthmatic patient treated with beclomethasone dipropionate. *Chest* 1977; **72**: 359–60.
3. Klotz LR, *et al.* The use of beclomethasone dipropionate inhaler complicated by the development of an eosinophilic pneumonia reaction *Ann Allergy* 1977; **39**: 133–6.
4. Mollura JL, *et al.* Pulmonary eosinophilia in a patient receiving beclomethasone dipropionate aerosol. *Ann Allergy* 1979; **42**: 326–9.

Hypersensitivity. There have been reports of asthmatic reactions to beclometasone dipropionate inhalations, possibly associated with materials used in their formulation or with the containers.[1-4]

1. Maddern PJ, *et al.* Adverse reaction after aerosol inhalation. *Med J Aus* 1978; **1**: 274.
2. Godin J, Malo JL. Acute bronchoconstriction caused by Beclovent and not Vanceril. *Clin Allergy* 1979; **9**: 585–9.
3. Clark RJ. Exacerbation of asthma after nebulised beclomethasone dipropionate. *Lancet* 1986; **ii**: 574–5.
4. Beasley R, *et al.* Benzalkonium chloride and bronchoconstriction. *Lancet* 1986; **ii**: 1227.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies beclometasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Reformulation. Reformulation of some metered-dose inhalers to use a chlorofluorocarbon (CFC)-free propellant has resulted in a change of efficacy. One CFC-free product (*Qvar, UK*) was reported to be effective at about half the dose[1] required with the CFC-containing product (see Use and Administration, p. 1621.2) and the UK CSM issued a reminder of the need for dosage reduction when converting from the conventional formulation to this product.[2] An open-label, crossover study in healthy subjects also found higher beclometasone plasma concentrations after use of another brand (*Beclazone, Eire*) of CFC-free product.[3]

However, this dose reduction does not apply to all CFC-free formulations of beclometasone,[4] and the UK MHRA has advised that such products should be prescribed by trade name.[5] A review[6] concluded that good studies on the bioequivalence between the reference beclometasone preparation and the newer CFC-free formulations were not available.

1. Davies RJ, *et al.* Hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol provides equivalent asthma control to chlorofluorocarbon beclomethasone dipropionate at approximately half the total daily dose. *Respir Med* 1998; **92** (suppl): 23–31.
2. CSM/MCA. Dose of CFC-free inhaled beclomethasone (Qvar). *Current Problems* 1999; **25**: 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023256&RevisionSelectionMethod=LatestReleased (accessed 06/07/06)
3. Lipworth BJ, Jackson CM. Pharmacokinetics of chlorofluorocarbon and hydrofluoroalkane metered-dose inhaler formulations of beclomethasone dipropionate. *Br J Clin Pharmacol* 1999; **48**: 866–8.
4. Anonymous. Switching to CFC-free beclometasone for asthma. *Drug Ther Bull* 2008; **46**: 46–8.
5. MHRA. Beclometasone dipropionate pressurised metered dose inhaler (issued 8th August 2006). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024433&RevisionSelectionMethod=LatestReleased (accessed 15/03/10)
6. Derom E, Pauwels RA. Pharmacokinetic and pharmacodynamic properties of inhaled beclometasone dipropionate delivered via hydrofluoroalkane-containing devices. *Clin Pharmacokinet* 2005; **44**: 815–36.

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Beclometasone is stated to be readily absorbed from sites of local application, and rapidly distributed to all body tissues. It is metabolised mainly in the liver, but also in other tissues including gastrointestinal tract and lung; enzymatic hydrolysis rapidly produces the monopropionate (which has some glucocorticoid activity), and, more slowly, the free alcohol, which is virtually devoid of activity. Only a small proportion of an absorbed dose is excreted in urine, the remainder being excreted in the faeces mainly as metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Airbeclosona†; Menaderm Simple; Propavent; Rectomenaderm; Rinosol; ***Austral.***: Beconase Allergy & Hayfever 12 Hour; Beconase†; Becotide†; Qvar; ***Austria***: Aerocortin; Beclomet; Becotide; ***Belg.***: Beclometasop†; Beclophar; Beconase†; Clipper; Qvar; ***Braz.***: Alerfin; Beclort; Beclosol; Clenil; Miflasona; ***Canad.***: Gen-Beclo†; Mylan-Beclo; Propaderm; Qvar; Rivanase; ***Chile***: Beclosema†; Destap; Filair†; Flumates†; ***China***: Beconase (伯克纳); Becotide (必可酮); Beikele (贝可乐); ***Cz.***: Aldecin†; Becloforte; Beclomet; Becodisks†; Beconase†; Becotide†; Clenil; Ecobec; Nasobec; ***Denm.***: AeroBec; Beclomet; Beconase; Fostair; ***Fin.***: AeroBec; Beclomet; Beclonasal; Beconase; ***Fr.***: Asmabec; Beclo-Rhino; Beclojet; Beclonet†; Beclospin; Beclospray; Beconase; Becotide; Bemedrex; Ecobec; Humex Rhume des Foins; Miflasone; Qvar; Qvarspray; Rhinomaxil; Rinoclenil; ***Ger.***: AeroBec†; Beclo†; Beclohexal†; Beclomet; Beclorhinol; Beconase Aquosum†; Bronchocort; Junik; Livocab direkt mit Beclometason†; ratioAllerg; Rhinivict; Sanasthmax; Sanasthmyl†; Ventolair; ***Gr.***: Beclomet; Becloneb; Beclospin; Becolex; Becotide; Bidiclin; Breathline; Clenil Forte Jet; Clenil Rino†; Clenil; Dermolate; Iriniozol; Qvar; Respocort; Rinosol; ***Hong Kong***: Beclate; Beclazone; Beconase; Cyclosonț; Nasobec; Qvar†; ***Hung.***: Beclonasal; ***India***: Becderm; Beclasone; Beclate; Becloair; Becloderm; Becoride; Belar; Cortisone-BM; Econase; ***Indon.***: Beclomet†; Beconase†; Becotide†; Cleniderm; ***Irl.***: Asmabec; Beclazone; Beclo-Rhino†; Becloneb; Beclospin; Beconase Hayfever; Beconase; Becotide; Nasobec; Qvar; ***Israel***: Qvar; Viarex†; ***Ital.***: Becotide; Bemedrex; Clenil; Clenilexx; Clipper; Inalone; Klosternal; Menaderm Simplex; Prontinal; Rino Clenil; Topster; Turbinal; ***Jpn***: Propaderm; Rhinocort; Salcoat; ***Malaysia***: Beclate; Beclazone; Beclomet; Beconase; Belax; Clenil; Qvar; ***Mex.***: Beclazone†; Beconase; Becotide†; Dobipro; Riferina; ***Neth.***: Beclodin†; Becloforte†; Qvar; ***Norw.***: AeroBec; Beclomet; Becotide†; ***NZ***: Alanase; Atomase; Beclazone; Beconase Hayfever; Qvar; Respocort; ***Philipp.***: Qvar†; ***Pol.***: Beclonasal; Becodisk†; Cortare; Nasobec†; ***Port.***: Beclotaide; Beconase; Clenil†; Ecobec; Qvar; ***Rus.***: Aldecin (Альдецин); Beclate (Беклат); Beclazone (Беклазон); Becloforte (Беклофорте)†; Beclojet (Беклоджет)†; Beclospir (Беклоспир); Becodisk (Бекодиск)†; Beconase (Беконазе)†; Becotide (Бекотид); Clenil (Кленил); Cycloson (Циклозон); Nasobec (Насобек); Rhinoclenil (Ринокленил); ***S.Afr.***: Beceze; Beclate; Becloforte†; Beconase; Becotide†; Ciplanaze; Clenil; Qvar; Ventnaze; ***Singapore***: Beclo Asma; Beclomet; Decomit; ***Spain***: Beclo Asma†; Beclo Rino; Becloenema; Becloforte; Beclosona†; Beconase; Becotide; Bidiclin; Clipper; Dereme†; Menaderm Simple; Recto Menaderm NP; ***Swed.***: AeroBec; Beclomet; Becotide; ***Switz.***: BECeco; Beclonarin†; Becodisk†; Beconase; Beconasol†; Qvar; ***Thai.***: Atomase†; Beclocip; Beclomet; Beconase; Bemase; Clenil; Qvar; Rino Clenil; ***Turk.***: Becloforte; Becodisks; Becotide†; Beklamet; Beklazon; Clenil; Filair; Rinoclenil; ***UAE***: Beclohale; ***UK***: AeroBec†; Asmabec; Beceze; Beclazone†; Beclogen; Becodisks†; Beconase; Clenil; Clipper; Filair; Hayfever Relief; Nasobec; Pollenase Nasal; Pulvinal Beclometasone Dipropionate; Qvar; Vivabec; ***Ukr.***: Beclazone (Беклязон); ***USA***: Beclovent; Beconase; Qnasl; Qvar; ***Venez.***: Beclofortil; Beclorino; Beclosil; Beconase; Biobeclasona; Biobeclod; Genbeclo; Nasair.

Multi-ingredient Preparations. *Arg.*: Beclasma; Biotaer Nebulizable; Butocort; Butosol†; Menaderm N; Salbutol Beclo; Ventide; ***Austria***: Formodual; Foster; ***Belg.***: Inuvair; ***Braz.***: Aerocort S; Aerotide; Clenil Compositum; Fostair; ***Chile***: Aero-Plus; Aerosoma†; Asmavent-B; Belomet; Butocort; Butotal B; Herolan Aerosol; Ventide; Cz.: Combair; Formodual†; ***Denm.***: Innovair; ***Fin.***: Innovair; ***Fr.***: Formodual; Innovair; ***Ger.***: Foster; Inuvair; ***Gr.***: Beclomycin; Foster; Inuvair; ***Hong Kong***: Ventide†; ***Hung.***: Foster; ***India***: Adcort; Advin-NC; Aerocort; Aerotide; Aerovent; Anocream; Arima; Atasol; Baclasia-CG; Baclasia-CN; BC-Zole; Becderm-N; Beciosal; Beclasone-C; Beclasone-GM; Beclate-C; Beclate-N; Beclocid-G; Beclocid; Beclocin-O; Becloderm-C; Becloderm-N; Beclolab-CG; Beclolab-NC; Beclomin; Beclomin; Beclotis-C; Beclotis-CG; Beclozen; Becmet-CG; Becmet-CG; Becmet-G; Becmet-GM; Becmet-N; Becmet-S; Bectop; Becze-N; Belar-G; Benda; Bestec; Bestonim C; Bestonim N; Bestopic-N; Bestopic; Bugderm; Candasia-B; Candibiotic; Candid B; Candiderma +; Candiderma; Candikit-N; Candivate; Canesten-S; Canison-B; Canison-BN; Canoderma; Cazol-B; CBL; CLCD; Cloben-G; Cloben; Clobiotic; Clocip B; Clocip NB; Clofung GM; Clofung-G; Clofung-N; Clofung; Clomax BN; Clomax-B; Clomax-BG; Clorid-B; CNB; Corge-C; Cuticare; Cutigard; Decand B; Decand BG; Derbec-N; Derisone; Dermaspan; Derminol; Diprogen; Drep; Durabec; Eclospan; Ecodax-G; Elderm; Eligao; Everbate; Evergum; Excan; Fubac; Fucin-B; Fudec-B; Fungi-BC; Fusiwal-B; Fuson-B; GCB; Gemiderm; Gentalene Plus; Gentalene-C; Ifydo-G; Imidil B; Imidil Plus; Infabact; Itchicos; Itchicure; Itchipol; Lamonte-BG; LBC; Leobet-GM; Leobet-NC; Leozole-B; Lotril-B; Lotril-BG; Mycoderm; Mycotic; Naderm RF; NC Derm; Neobate; Nifugal-B; Nivate-NC; Nuforce-GM; Olotic; Onderm; Otek-AC Plus; Otichek; Otiden; Otiderm; Otiflox; Otocin-O; Otocin; Otocos; Otosym; Pilovate; Sigmaderm; Stecort-NM†; Translipo-Triple; ***Indon.***: Ventide†; ***Ital.***: Clenil Compositum; Formodual; Foster; Inuver; Menaderm; ***Malaysia***: Aerocort; ***Mex.***: Ventide; ***Neth.***: Formodual; Foster; ***Norw.***: Inuxair; ***Philipp.***: Candibec; Combiderm; ***Pol.***: Fostex; ***Port.***: Formodual; Foster; ***Rus.***: Candibiotic (Кандибиотик); Candid B (Кандид Б); Candiderm (Кандидерм); Foster (Фостер); ***Spain***: Butosol; Formodual; Foster; Menaderm Clio; Menaderm Neomicina; Menaderm Otologico; ***Swed.***: Innovair; ***Thai.***: Beclosal; Clenil Compositum†; ***Turk.***: Belogent; Clenil Kompoze; Foster; Innovair; Ventide; ***UK***: Fostair; ***Ukr.***: Candibiotic (Кандибиотик); Candid B (Кандид-Б); Candiderm (Кандидерм); ***Venez.***: Aerocort; Beclosal; Butosol; Venticort; Ventide.

Pharmacopoeial Preparations

BP 2014: Beclometasone Aqueous Nasal Spray; Beclometasone Cream; Beclometasone Inhalation Powder, pre-dispensed; Beclometasone Inhalation Powder; Beclometasone Ointment; Beclometasone Pressurised Inhalation.

Betamethasone *(BAN, USAN, rINN)* ⊗

Betametasoni; Betadexamethasone; Betametason; Betametasona; Betametazon; Betametazonas; Betamethason; Bétaméthasone; Betamethasonum; Flubenisolone; Flubenisolonum; 9α-Fluoro-16β-methylprednisolone; β-Methasone; NSC-39470; Sch-4831; Бетаметазон.

9α-Fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_5$=392.5

CAS — 378-44-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QD07XC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS01CB04; QS02BA07; QS03BA03.

UNII — 9842X06Q6M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. Protect from light.

USP 36: (Betamethasone). A white to practically white, odourless, crystalline powder. Soluble 1 in 5300 of water, 1 in 65 of alcohol, 1 in 15 of warm alcohol, 1 in 325 of chloroform, and 1 in 3 of methyl alcohol; sparingly soluble in acetone and in dioxan; very slightly soluble in ether. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Acetate *(BANM, rINNM)* ⊗

Acetato de betametasona; Betametasoniasetaatti; Betametasona, acetato de; Betametasonacetat; Betametazon Asetat; Betametazon-acetát; Betametazono acetatas; Betamethasonacetat; Betamethason-acetát; Bétaméthasone, Acétate de; Betamethasoni Acetas; Бетаметазона Ацетат.

Betamethasone 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 987-24-6.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — TI05AO53LZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Betamethasone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in dichloromethane; freely soluble in acetone. It shows polymorphism. Protect from light.

USP 36: (Betamethasone Acetate). A white to creamy-white, odourless powder. Soluble 1 in 2000 of water, 1 in 9 of alcohol, and 1 in 16 of chloroform; freely soluble in acetone. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Benzoate

(BANM, USAN, rINNM) ⊗

Benzoato de betametasona; Betametasona, benzoato de; Bétaméthasone, Benzoate de; Betamethasoni Benzoas; W-5975; Бетаметазона бензоат.

Betamethasone 17α-benzoate.

$C_{29}H_{33}FO_6$=496.6

CAS — 22298-29-9.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — 877K0XW47A.

Pharmacopoeias. In *US*.

USP 36: (Betamethasone Benzoate). A white to practically white, practically odourless, powder. Insoluble in water; soluble in alcohol, in chloroform, and in methyl alcohol. Store in airtight containers at a temperature between 2 degrees and 30 degrees.

Betamethasone Dipropionate

(BANM, USAN, rINNM) ⊗

Beetametasonidipropionaatti; Betametasona, dipropionato de; Betametasondipropionat; Betametazon Dipropiyonat; Betametazon-dipropionát; Betametazono dipropionatas; Betametazonu dipropionian; Betamethasondipropionat; Betamethason-dipropionát; Bétaméthasone, Dipropionate de; Betamethasoni Dipropionas; Dipropionato de betametasona; Sch-11460; Бетаметазона дипропионат.

Betamethasone 17α,21-dipropionate.

$C_{28}H_{37}FO_7$=504.6

CAS — 5593-20-4.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — 826Y60901U.

NOTE. Compounded preparations of betamethasone dipropionate may be represented by the following names:

- Co-climasone (*PEN*)—clotrimazole and betamethasone dipropionate.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone Dipropionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Betamethasone Dipropionate). A white to cream-white, odourless powder. Insoluble in water; sparingly soluble in alcohol; freely soluble in acetone and in chloroform. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Betamethasone Sodium Phosphate

(BANM, rINNM) ⊗

Beetametasoninatriumfosfaatti; Betametasona, fosfato sódico de; Betametasonnatrifosfatum; Betametazon Disodyum Fosfat; Betametazon-nátrium-foszfát; Betametazono natrio fosfatas; Betamethasondihydrogenphosphat Dinatrium; Bétaméthasone Disodium Phosphate; Bétaméthasone, phosphate sodique de; Betamethason-fosfát sodná sůl; Betamethasoni natrii phosphas; Fosfato sódico de betametasona; Natrii Betamethasoni Phosphas; Натрия Бетаметазона Фосфат.

Betamethasone 21-(disodium phosphate).

$C_{22}H_{28}FNa_2O_8P$=516.4

CAS — 360-63-4 (betamethasone phosphate); 151-73-5 (betamethasone sodium phosphate).

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.
ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.
UNII — 7BK02SCT3W.

NOTE. **BET** is a code approved by the BP 2014 for use on single unit doses of eye drops containing betamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Betamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.0. Store in airtight containers. Protect from light.

USP 36: (Betamethasone Sodium Phosphate). A white to practically white, odourless, hygroscopic, powder. Soluble 1 in 2 of water and 1 in 470 of alcohol; freely soluble in methyl alcohol; practically insoluble in acetone and in chloroform. Store in airtight containers.

Betamethasone Valerate

(BANM, USAN, rINNM) ⊗

Betametasonivaleraatti; Betametasona, valerato de; Betametasonvalerat; Betametazon Valerat; Betametazono valeratas; Betametazonu walerianian; Betametazon-valerát; Bétaméthasone, valérate de; Betamethasoni Valeras; Betamethasonvalerat; Betamethason-valerát; Valerato de betametasona; Бетаметазона валерат.

Betamethasone 17α-valerate.

$C_{27}H_{37}FO_6$=476.6

CAS — 2152-44-5.

ATC — A07EA04; C05AA05; D07AC01; H02AB01; R01AD06; R03BA04; S01BA06; S02BA07; S03BA03.

ATC Vet — QA07EA04; QC05AA05; QD07AC01; QH02AB01; QR01AD06; QR03BA04; QS01BA06; QS02BA07; QS03BA03.

UNII — 9IFASXM7R2.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Betamethasone Valerate). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

USP 36: (Betamethasone Valerate). A white to practically white, odourless, powder. Practically insoluble in water; soluble 1 in 16 of alcohol, 1 in less than 10 of chloroform, and 1 in 400 of ether; freely soluble in acetone; slightly soluble in benzene. Store in airtight containers.

Uses and Administration

Betamethasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); the anti-inflammatory activity of 750 micrograms of betamethasone is equivalent to about 5 mg of prednisolone. It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p. 1597.3), except adrenal-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. Its virtual lack of mineralocorticoid properties makes betamethasone particularly suitable for treating conditions in which water retention would be a disadvantage.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 1 mg of betamethasone:

- betamethasone acetate 1.1 mg
- betamethasone benzoate 1.3 mg
- betamethasone dipropionate 1.3 mg
- betamethasone sodium phosphate 1.3 mg
- betamethasone valerate 1.2 mg

However, esterification generally alters potency and compounds with equivalent betamethasone content may not have equivalent clinical effect.

When given orally betamethasone or betamethasone sodium phosphate are used; the usual dose, expressed in terms of betamethasone, ranges from 0.5 to 5 mg daily.

For **parenteral** use the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection in doses equivalent to 4 to 20 mg of betamethasone. Doses may be repeated 3 or 4 times in 24 hours if necessary, depending on the condition being treated and the clinical response. It may also be given by local injection into soft tissues in doses equivalent to 4 to 8 mg of betamethasone. The dose may be repeated on 2 or 3 occasions, according to patient response. The sodium phosphate ester is also sometimes used with the acetate or dipropionate esters, which have a slower and more prolonged action. These suspensions may be given by intramuscular injection for a systemic effect, or by intra-articular, soft-tissue, or intralesional injection for local therapy.

For doses used in children, see below.

Betamethasone sodium phosphate is also used in the **topical** treatment of allergic and inflammatory conditions of the eyes, ears, or nose, usually as drops or ointment containing 0.1%.

For topical application in the treatment of various skin disorders the dipropionate and valerate esters of betamethasone are extensively used in creams, ointments, lotions, and scalp applications. The usual concentrations available are the equivalent of 0.05% of betamethasone as the dipropionate, and 0.025 or 0.1% as the valerate. A medicated plaster containing betamethasone valerate is also available. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Betamethasone valerate has also been used by **inhalation** for the prophylaxis of asthma.

Other esters of betamethasone which have occasionally been used include the benzoate, butyrate propionate, phosphate, salicylate (cortobenzolone), and valero-acetate.

Betamethasone adamantoate has been used in veterinary practice.

Administration in children. For parenteral use betamethasone sodium phosphate may be given intravenously by injection or infusion. It may be given to provide the following doses equivalent to betamethasone:

- infants aged up to 1 year: 1 mg
- 1 to 5 years: 2 mg
- 6 to 12 years: 4 mg
- 12 years and older: adult doses (see above)

Doses may be repeated 3 or 4 times in 24 hours if necessary, depending on the condition being treated and the clinical response.

Haemangioma. For reference to the use of a mixture of betamethasone and triamcinolone for the intralesional injection of haemangiomas, see p. 1605.3.

Inflammatory bowel disease. For a comparison of betamethasone and beclometasone enemas in the treatment of ulcerative colitis, see under Beclometasone, p. 1622.1. Corticosteroids are one of the mainstays of treatment of inflammatory bowel disease, the general management of which is discussed on p. 1808.3.

Neonatal respiratory distress syndrome. For a discussion on the antenatal use of betamethasone to prevent neonatal respiratory distress syndrome, see p. 1608.3.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Betamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Anosmia. Complete anosmia was reported in 2 patients after the use of nasal drops containing betamethasone and neomycin sulfate[1] and, in one patient, showed no sign of resolving 1 year later. The reaction was thought to be due to the preservative thiomersal present in the drops, although it was noted that neomycin could exert a toxic effect on the olfactory mucosa and that there have been several reports of anosmia associated with the use of betamethasone alone.

1. Whittet HB, *et al.* Anosmia due to nasal administration of corticosteroid. *BMJ* 1991; **303**: 651.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies betamethasone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Betamethasone crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bactisona; Betacort; Betacort; Betacort; Betasone-G 12 Horas; Betasone-G; Betatopic; Betnovate Capilar; Betnovate; Biocur; Blacor; Butasona RL; Butasona; Celestone Cronodose; Celestone; Cevicort NC; Cevicort; Cold; Corteroid Retard; Corteroid; Corticas Retard; Corticas; Cortiderma; Cortimart†; Crono Corticas; Cronobetacort; Cronocorteroid; Cronodicasone Depot; Cronodicasone; Cronolevel; Deltalaf; Depocort Crono; Depocort Retard; Depocort; Dermizol; Dicasone; Difenac Forte; Diprosone; Lazar-Cort; Metamar; Micosep B; Quiacort; Rapi-Betacort; Transderma B; Valederm; Vitacortil B; *Austral.*: Antroquoril; Betnovate; Celestone Chronodose; Celestone M; Cortival; Diprosone; Eleuphrat; *Austria*: Betnesol; Betnovate; Celestan; Diproderm; Diproforte; Diprophos; Solu-Celestan; *Belg.*: Betnelan-V; Betnesol; Celestone Chronodose; Celestone; Diprolene; Diprosone; *Braz.*: Beclonato; Benevat; Beta Long; Betaderm; Betametagen; Betaprospan; Betaspan; Betatrinta; Betnelan; Betnolon; Betnovate; Betrat B; Betrospam; Betsona; Celestone Soluspan; Celestone; Dermatisan; Diprobeta; Diprocort; Diprosen; Diprosone; Diprospan; Duoflam; Koide; Sensitex†; Valbet; *Canad.*: Betaderm; Betaject; Betnesol; Celestoderm; Celestone Soluspan; Diprolene; Diprosone; Luxiq; Prevex B; ratio-Ectosone; ratio-Topilene; ratio-Topisone; Rivasone; Rolene; Rosone; Taro-Sone; Valisone; *Chile*: Cidoten Rapilento; Cidoten V; Cidoten; Coritex; Cremirit; Cronolevel; Dacam RL; Dacam; Diprolene†; Diprospan; Diprospan; Dispranil; Esancort; Konicortil; Labosona; Oftasona P; Spel†; *China*: Bei Shi Li (贝施利); Beisong (倍松); Diprospan (得宝松); Li Yan Jia (力言佳); Zheng Tuo (正妥); *Cz.*: Beloderm; Betesil; Betnovate; Diprophos; Diprosone; Kuterid; *Denm.*: Betnovat; Betnovate; Bettamousse; Celeston; Celeston; Diproderm; Diprofos; Diprolen; Diprospan; *Fin.*: Bemetson; Betapred; Betnovat; Bettamousse; Celestoderm; Celeston Chronodose; Diproderm; Diprolen; *Fr.*: Betesil; Betnesol; Betneval; Buccobet; Celestene Chronodose; Celestene; Celestoderm†; Diprolene; Diprosone; *Ger.*: Bemon; Betacreme†; Betagalen; BetaLotio†; BetaSalbe†; Betnesalic mono†; Betnesol-V; Betnesol; Celestamine N; Celestan Depot; Celestan solubile; Celestan-V; Cordes Beta; Deflatop; Diprosis; Diprosone Depot; Diprosone; Linolacort Beta; Soderm; *Gr.*: Alo-Haar; Bagocot†; Betamatic; Betatape; Betnesol; Betnovate; Celestene; Celestoderm-V; Celestone Chronodose; Celestone; Flogozyme; Galinocort; Helpoderm; Iraciton†; Locason-N†; Locason; Movithiol; Osmoran; Propiochrone; Propioform; Sanorvil; *Hong Kong*: Beprogel; Beprosone; Betasone; Betnovate; Betowel†; CP-Betasone†; Derzid; Diprocel; Diprosone; Diprospan; Synmethasone†; Uniflex†; *Hung.*: Betesil; Diprophos; *India*: Acticard; Belar; Belsone; Ben; Benicort; Betacortril; Betafoam; Betagel; Betalar; Betamil; Betamine; Betariv; Betawin; Betnecip; Betnecort; Betnederm; Betnelan; Betnesol; Betni; Betnovate; Betsone; Bevent; Celestone; Cortiderm; Cortil; Diplene; Diprovate; Glosone; Lupiderm; Milbeta; Ocusone; Topicasone; Valbet; Walacort; *Indon.*: Benoson; Betam-Ophtal; Betason; Betnovate†; Betodermin; Betopic; Celestoderm-V; Celestone; Corsaderm; Diprosone-OV; Exabet†; Mesonta†; Metonate; Molason; Oviskin; Proson†; Protocort; Scanderma; Skizon†; Vason†; *Irl.*: Betacap; Betnelan†; Betnesol; Betnovate; Bettamousse; Diprosone; *Israel*: Betacap; Betacorten; Betnesol; Betnovate; Bettamousse; Celestone Chronodose; Diprolene†; Diprosone†; Diprospan; *Ital.*: Beben; Betnelan; Beta 21; Betamesol; Betesil; Bettamousse; Celestone Cronodose; Celestone; Cortiflam; Diprosone; Ecoval; *Malaysia*: Beavate; Benosone; Beprogel; Beprosone; Besone; Beta; Betamet; Betasone; Betnosone†; Betnovate; Bufencon; Daivobet; Dibetasol†; Diprocel; Diprosone; Diprospan; Uniflex; *Mex.*: Betnovate; Celestone Soluspan; Celestone; Cronolevel; Dermoval; Diprofast; Dipronova†; Diprosone†; Diprospan; Disons Dex; Erispan; Reubaxona; *Neth.*: Betnelan; Betnesol; Celestoderm†; Celestone Chronodose; Celestone; Diprolene; Diprosone; *Norw.*: Betnovat; Bettamousse; Celeston; Diproderm; *NZ*: Beta; Betnesol; Betnovate; Bivate; Celestone Chronodose; Diprolene†; Diprosone; *Philipp.*: Beprosone; Beta-D; Beta; Betaderm; Betnelan; Betnovate; Celestone; Diprolene; Diprosone; Diprospan; Hoebenate; Innodesone; Steroderm; *Pol.*: Beloderm; Celestone; Diprolene; Diprophos; Diprosone†; Kuterid; *Port.*: Betnovate; Celesdepot; Celestone; Cilestoderme; Diprolos; Diprosone; Soluderme; *Rus.*: Akriderm (Акридерм); Beloderm (Белодерм); Betasone (Бетазон); Celestoderm-V (Целестодерм-В); Celestone (Целестон); Diprospan (Диprospан); Flosteron (Флостерон); *S.Afr.*: Betanoid; Betnesol; Betnovate; Celestone Soluspan; Celestone; Diprosone; Lenasone; Lenovate; Persivate Repivate; Steromien; Topivate; *Singapore*: Beprogel; Beprosone; Besone; Betacorten†; Betasone; Betnovate; Camnovate Dermasone; Derzid; Dibetasol; Diprocel; Diprosone; Diprospan HD-Betasone; Medobeta; SP-Betasone; Synmethasone; Uniflex *Spain*: Betnovate; Bettamousse; Celestoderm-V; Celestone Cronodose; Diproderm; *Swed.*: Betapred; Betnoderm†; Betnovat Bettamousse; Celeston bifas; Celeston valerat†; Diproderm Diprolen; *Switz.*: Betnesol; Betnovate; Celestoderm-V†; Celestone Chronodose; Celestone†; Diprolene; Diprosone; *Thai.* Beprogel; Bepronate; Beprosone; Besone; Bessasone†; Beta Betacort; Betama; Betameth; Bethasone; Betnovate; Betosone Bipro†; Clinivate; Derzid; Diprobet; Diprosone; Diprospan Diprotop; Hofra B; Polynovate; Sebo; TM Bet; Valbet; Valerbet *Turk.*: Betnovate; Celestoderm-V; Celestone Chronodose; Dermabel; Dermakord; Diprolene; Diprospan; Novovate; Serederm *UAE*: Betasone; Betasone; *UK*: Betacap; Betesil; Betnelan† Betnesol; Betnovate RD (Ready Diluted); Betnovate; Betta mousse; Diprosone; Vista-Methasone; *Ukr.*: Betaspan

(Бетаспан); Celestoderm (Целестодерм); Celeston (Целестон); Diprospan (Дипроспан); Flosteron (Флостерон); Mesoderm (Мезодерм); *USA*: Beta-Val; Cel-U-Jec; Celestone Soluspan; Celestone; Diprolene; Diprosone†; Luxiq; Maxivate; Valisone; *Venez.*: Beprospen; Betacort; Betaderm; Betagen Solspen; Betagen; Betnovate; Celestoderm; Celestone Soluspan; Celestone; Diprocel; Diprosone; Diprospan; Itisona.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Betamethasone and Clioquinol Cream; Betamethasone and Clioquinol Ointment; Betamethasone Eye Drops; Betamethasone Injection; Betamethasone Sodium Phosphate Tablets; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Betamethasone Valerate Scalp Application;

USP 36: Betamethasone Benzoate Gel; Betamethasone Cream; Betamethasone Dipropionate Cream; Betamethasone Dipropionate Lotion; Betamethasone Dipropionate Ointment; Betamethasone Dipropionate Topical Aerosol; Betamethasone Oral Solution; Betamethasone Sodium Phosphate and Betamethasone Acetate Injectable Suspension; Betamethasone Sodium Phosphate Injection; Betamethasone Syrup; Betamethasone Tablets; Betamethasone Valerate Cream; Betamethasone Valerate Lotion; Betamethasone Valerate Ointment; Clotrimazole and Betamethasone Dipropionate Cream.

Budesonide *(BAN, USAN, rINN)* ⊗

Budesonid; Budesónida; Budésonide; Budesonidi; Budesonidum; Budezonid; Budezonidas; S-1320; Будезонид.

An epimeric mixture of the α- and β-propyl forms of 16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione.

$C_{25}H_{34}O_6$=430.5

CAS — 51333-22-3 (11β,16α); 51372-29-3 (11β,16α(R)); 51372-28-2 (11β,16α(S)).

ATC — A07EA06; D07AC09; H02AB16; R01AD05; R03BA02.

ATC Vet — QA07EA06; QD07AC09; QR01AD05; QR03BA02.

UNII — Q3OKS62Q6X (11β,16α(RS)); 168L5HT37P (11β,16α(S)).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Budesonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane.

USP 36: (Budesonide). A white to off-white, odourless, crystalline powder. Practically insoluble in water and in heptane; sparingly soluble in alcohol; freely soluble in chloroform. Store in airtight containers at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Budesonide is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is used by inhalation in the management of **asthma** (below), in usual doses of 400 micrograms daily in 2 divided doses from a metered-dose aerosol; in severe asthma the dosage may be increased up to a total of 1.6 mg daily, and guidelines for the management of asthma permit up to 2 mg daily. Maintenance doses may be less than 400 micrograms daily but should not be below 200 micrograms daily. Budesonide is also available for the management of asthma in the form of a dry powder inhaler; doses are 200 to 800 micrograms daily, as 2 divided doses or a single daily dose; up to 800 micrograms twice daily may be given if necessary. Patients for whom budesonide from a pressurised inhaler or dry powder formulation is unsatisfactory may use a nebulised solution. The usual starting dose when asthma is severe, or while reducing or stopping oral corticosteroids, is 1 to 2 mg inhaled twice daily. This may be increased if asthma is very severe. Maintenance doses are 0.5 to 1 mg inhaled twice daily.

Budesonide is used intranasally for the prophylaxis and treatment of **rhinitis** (p. 612.1). In the UK, two nasal spray preparations are available, one containing 100 micrograms per metered spray, and one containing 64 micrograms per metered spray. The initial recommended dose is either 2 sprays into each nostril once daily in the morning, or 1 spray into each nostril twice daily. This may be subsequently reduced to 1 spray into each nostril once daily; treatment can be continued for up to 3 months. In the USA, a nasal spray delivering 32 micrograms of budesonide per actuation is available. The recommended initial dose is 1 spray into each nostril once daily, increasing as necessary up to a maximum of 4 sprays in each nostril once daily. The dose should then be reduced to the lowest effective dose that maintains control of symptoms.

Budesonide is also used as a nasal spray in the management of **nasal polyps** (p. 1608.2). In the UK, 1 spray (containing 64 or 100 micrograms, as above) is given into each nostril twice daily for up to 3 months. As an alternative, some preparations containing doses of 64 micrograms may be given as 2 sprays into each nostril once daily.

Locally-acting formulations of budesonide are used in the management of **inflammatory bowel disease** (see below). In mild to moderate Crohn's disease affecting the ileum or ascending colon it is given orally as modified-release capsules intended for a topical effect on the gastrointestinal tract. The recommended dose is 9 mg daily for active disease, as either a single dose before breakfast or in 3 divided doses about 30 minutes before meals, depending on the preparation. Treatment is given for up to 8 weeks, and the dosage should be reduced 2 to 4 weeks before discontinuing therapy. For recurring episodes of active Crohn's disease, an 8-week course may be repeated. After an 8-week course for active disease, budesonide 6 mg once daily is recommended for maintenance of clinical remission, for up to 3 months; thereafter, doses are tapered and therapy stopped, as continued treatment has not shown substantial clinical benefit. There is some absorption of budesonide from the gastrointestinal tract, and the dose may need to be reduced in patients with hepatic impairment, especially those with cirrhosis (see also Hepatic Impairment, p. 1626.2). Ulcerative colitis affecting the rectum and sigmoid colon may be treated locally with budesonide. A retention enema providing a dose of 2 mg in 100 mL is given daily at bedtime for 4 weeks, which may be extended to 8 weeks if the patient is not in remission after the initial 4-week course. Alternatively, a rectal foam can be used in a dose of 2 mg once daily, usually for 6 to 8 weeks. The dose may be given in the morning or the evening, but treatment is more effective if the bowel is emptied before a dose is given.

Locally-acting formulations of budesonide are also used in the management of **collagenous colitis** (see Microscopic Colitis, p. 1626.1). It is given orally as modified-release capsules in a dose of 3 mg three times daily for up to 8 weeks. The dosage should be reduced gradually during the last 2 weeks of therapy.

A viscous oral formulation of budesonide is under investigation for the local treatment of **eosinophilic oesophagitis** (p. 1807.1).

Budesonide is used topically in the treatment of various **skin disorders**, as a cream, lotion, or ointment containing 0.025%. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, including the use of budesonide in childhood **croup**, see below.

General reviews.

1. Brogden RN, McTavish D. Budesonide: an updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 1992; 44: 375–407 and 1012.
2. Hvizdos KM, Jarvis B. Budesonide inhalation suspension: a review of its use in infants, children and adults with inflammatory respiratory disorders. *Drugs* 2000; 60: 1141–78.
3. Stanaland BE. Once-daily budesonide aqueous nasal spray for allergic rhinitis: a review. *Clin Ther* 2004; 26: 473–92.

Administration. *INHALATIONAL ROUTE.* One study in 6 children aged up to 30 months found that about 75% of the nominal dose of nebulised budesonide was deposited in the nebuliser system,[1] while a study in 126 older children indicated that maintenance doses of budesonide could be halved when the dose was given by dry powder inhaler rather than nebuliser, without any loss of asthma control.[2] Although oropharyngeal deposition is thought to play a role in the systemic effects of inhaled corticosteroids, another study[3] indicated that only about 20% of the systemically available drug appeared to be derived from oropharyngeal deposition after inhalation from a dry powder inhaler.

There is evidence that the timing of inhaled therapy might influence some systemic effects. A study[4] in children with mild asthma found that 800 micrograms of budesonide inhaled in the morning had less effect on measurements of short-term growth and collagen turnover than inhalation of 400 micrograms twice daily.

1. Carlsen KCL, *et al.* How much nebulised budesonide reaches infants and toddlers? *Arch Dis Child* 1992; 67: 1077–9.
2. Agertoft L, Pedersen S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993; 69: 130–3.
3. Pedersen S, *et al.* The influence of orally deposited budesonide on the systemic availability of budesonide after inhalation from a Turbuhaler. *Br J Clin Pharmacol* 1993; 36: 211–14.
4. Heuck C, *et al.* Adverse effects of inhaled budesonide (800 micrograms) on growth and collagen turnover in children with asthma: a double-blind comparison of once-daily versus twice-daily administration. *J Pediatr* 1998; 133: 608–12.

Administration in children. Budesonide is used by inhalation in the management of **asthma** in children. Using a metered-dose aerosol, children aged from 2 to 12 years old may be given 200 to 800 micrograms daily, in divided doses. A dry powder inhaler, which is breath-actuated, may be used in children aged 5 years and older in doses of 200 to 800 micrograms daily in 2 divided doses. Daily doses of up to 400 micrograms may be given as a single daily dose. If these methods of delivery are unsatisfactory, a nebulised solution may be used. For children between 3 months and 12 years of age, an initial dose of 0.5 to 1 mg twice daily may be given. The maintenance dose is usually 250 to 500 micrograms twice daily, but a dose of 250 micrograms once daily may be adequate.

Budesonide is also given by inhalation as a nebulised solution in the management of childhood **croup** (p. 1603.3). The usual dose is 2 mg, as a single inhaled dose or as 2 doses of 1 mg given 30 minutes apart.

Budesonide may be used intranasally in the prophylaxis and treatment of allergic **rhinitis** in children aged 6 years and older. In the UK, a nasal spray containing 64 micrograms per metered spray may be used in similar doses to those used in adults (see Uses and Administration, above). In the USA, the recommended initial dose of a spray delivering 32 micrograms per actuation is 1 spray into each nostril once daily, increasing as necessary to a maximum of 2 sprays into each nostril once daily. The dose should then be reduced to the lowest effective dose that maintains control of symptoms.

In the UK, a nasal spray containing 64 micrograms per metered spray may also be given in similar doses to those used in adults (see Uses and Administration, above) for the management of **nasal polyps** in children aged 6 years and older.

Asthma. Corticosteroids and $beta_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

References to the use of budesonide in asthma.[1-7] Its use as a fixed-dose combination with formoterol has also been reviewed.[8-10]

1. Baker JW, *et al.* A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics* 1999; 103: 414–21.
2. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000; 343: 1054–63.
3. Leflein JG, *et al.* Nebulized budesonide inhalation suspension compared with cromolyn sodium nebulizer solution for asthma in young children: results of a randomized outcomes trial. *Pediatrics* 2002; 109: 866–72.
4. Pauwels RA, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071–6.
5. FitzGerald JM, *et al.* Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004; 59: 550–6.
6. Berger WE, *et al.* Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. *J Pediatr* 2005; 146: 91–5.
7. Berger WE. Budesonide inhalation suspension for the treatment of asthma in infants and children. *Drugs* 2005; 65: 1973–89.
8. Goldsmith DR, Keating GM. Budesonide/formoterol: a review of its use in asthma. *Drugs* 2004; 64: 1597–1618.
9. McCormack PL, Lyseng-Williamson KA. Budesonide/formoterol: a review of its use as maintenance and reliever inhalation therapy in asthma. *Drugs* 2007; 67: 2407–31.
10. Lyseng-Williamson KA, Simpson D. Budesonide/formoterol pressurized metered-dose inhaler. *Drugs* 2008; 68: 1855–64.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1). The use of a fixed-dose combination of budesonide and formoterol has been reviewed.[1,2]

1. Reynolds NA, *et al.* Budesonide/formoterol: in chronic obstructive pulmonary disease. *Drugs* 2004; 64: 431–41.
2. Lyseng-Williamson KA. Budesonide/formoterol pressurized metered-dose inhaler: in chronic obstructive pulmonary disease. *Drugs* 2009; 69: 1459–70.

Cystic fibrosis. Cystic fibrosis (p. 177.2) is associated with bronchial hyper-responsiveness; a small study[1] has suggested that inhalation of budesonide 1.6 mg daily for 6 weeks improves hyper-responsiveness slightly and leads to improvement in cough and dyspnoea. A larger study[2] of budesonide given for two successive 3-month treatment periods found improved hyper-responsiveness and a trend towards slower decline in lung function.

1. Van Haren EHJ, *et al.* The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. *Respir Med* 1995; 89: 209–14.
2. Bisgaard H, *et al.* Controlled trial of inhaled budesonide in patients with cystic fibrosis and chronic bronchopulmonary Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med* 1997; 156: 1190–6.

Inflammatory bowel disease. Budesonide has been given as an enema for the treatment of distal ulcerative colitis, in which context its potency and low systemic availability are advantageous.[1] A rectal foam has also been developed, which may be easier to use, and retain in the bowel, than an enema.[2] Budesonide is available as a modified-release oral dosage form for the management of active Crohn's disease.[1,3] Ileal-release preparations of budesonide have been indicated as first-line therapy in the treatment of mild to moderate ileal and right-sided colonic Crohn's disease.[4] Systematic review[5] has suggested that it is slightly less effective than conventional corticosteroid therapy, but is associated with fewer adverse effects. Budesonide has also been effective in delaying relapse in quiescent disease.[6-8] However, the benefit appears to be short-term (3 months)[4] and it has been concluded that oral modified-release budesonide is not effective in long-term (12

months) maintenance of remission.[4,9] Similarly, oral budesonide was ineffective in preventing postoperative recurrence after resection for Crohn's disease.[10]

For a discussion of inflammatory bowel disease, see p. 1808.3.

1. Spencer CM, McTavish D. Budesonide: a review of its pharmacological properties and therapeutic efficacy in inflammatory bowel disease. *Drugs* 1995; 50: 854–72.
2. Gross V, *et al.* Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; 23: 303–12.
3. McKeage K, Goa KL. Budesonide (Entocort EC capsules): a review of its therapeutic use in the management of active Crohn's disease in adults. *Drugs* 2002; 62: 2263–82.
4. Lichtenstein GR, *et al.* American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006; 130: 935–9. Also available at: http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508506000734.pdf (accessed 22/09/06)
5. Seow CH, *et al.* Budesonide for induction of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2008 (accessed 22/08/08).
6. Greenberg GR, *et al.* Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled dose-ranging study. *Gastroenterology* 1996; 110: 45–51.
7. Löfberg R, *et al.* Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease: a placebo controlled one year study. *Gut* 1996; 39: 82–6.
8. Gross V, *et al.* Low dose oral pH modified release budesonide for maintenance of steroid induced remission in Crohn's disease. *Gut* 1998; 42: 493–6.
9. Benchimol EI, *et al.* Budesonide for maintenance of remission in Crohn's disease. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 12/03/10).
10. Hellers G, *et al.* Oral budesonide for prevention of postsurgical recurrence in Crohn's disease. *Gastroenterology* 1999; 116: 294–300.

Microscopic colitis. Budesonide has been studied in the treatment of microscopic colitis (p. 1811.1). It has been used in a few small controlled studies[1-5] of the management of collagenous colitis. Treatment courses given orally for 6 or 8 weeks were found to improve symptoms and histology, and the short-term benefits have been confirmed by meta-analysis,[6] although high rates of relapse after stopping treatment have been reported.[3,5] Treatment for up to 6 months has been reported to maintain remission,[7,8] but the risk of relapse is still high after therapy is stopped.[6]

Oral budesonide has also been studied with some success in a small number of patients with lymphocytic colitis.[9]

1. Baert F, *et al.* Budesonide in collagenous colitis: a double-blind placebo-controlled trial with histologic follow-up. *Gastroenterology* 2002; 122: 20–5.
2. Miehlke S, *et al.* Budesonide treatment for collagenous colitis: a randomized, double-blind, placebo-controlled, multicenter trial. *Gastroenterology* 2002; 123: 978–84.
3. Bonderup OK, *et al.* Budesonide treatment of collagenous colitis: a randomised, double blind, placebo controlled trial with morphometric analysis. *Gut* 2003; 52: 248–51.
4. Madisch A, *et al.* Oral budesonide therapy improves quality of life in patients with collagenous colitis. *Int J Colorectal Dis* 2005; 20: 312–16.
5. Miehlke S, *et al.* Long-term follow-up of collagenous colitis after induction of clinical remission with budesonide. *Aliment Pharmacol Ther* 2005; 22: 1115–19.
6. Peyen B, *et al.* Meta-analysis: budesonide treatment for collagenous colitis. *Aliment Pharmacol Ther* 2004; 20: 745–9.
7. Miehlke S, *et al.* Oral budesonide for maintenance treatment of collagenous colitis: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 2008; 135: 1510–16.
8. Bonderup OK, *et al.* Long-term budesonide treatment of collagenous colitis: a randomised, double-blind, placebo-controlled trial. *Gut* 2009; 58: 68–72.
9. Miehlke S, *et al.* Budesonide is effective in treating lymphocytic colitis: a randomized double-blind placebo-controlled study. *Gastroenterology* 2009; 136: 2092–2100.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Inhalation of high doses of budesonide is associated with some adrenal suppression. Systemic absorption may follow nasal use, particularly after high doses or prolonged treatment. The dose of oral budesonide may need to be reduced in hepatic impairment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Reviews.

1. Christensson C, *et al.* Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. *Drug Safety* 2008; 31: 965–88.

Effects on the bones. For mention of the effects of inhaled budesonide on markers of collagen turnover and bone density in asthmatic children, see under Adverse Effects of Beclometasone, p. 1622.2. For the suggestion that inhalation once-daily in the morning may have less marked effects on growth and collagen turnover than twice-daily inhalation, see Administration, p. 1625.2.

Effects on the nervous system. Psychotic behaviour has been reported after use of inhaled budesonide.[1-3]

1. Lewis LD, Cochrane GM. Psychosis in a child inhaling budesonide. *Lancet* 1983; ii: 634.
2. Meyboom RHB, de Graff-Breederveld N. Budesonide and psychic side effects. *Ann Intern Med* 1988; 109: 683.
3. Connett G, Lenney W. Inhaled budesonide and behavioural disturbances. *Lancet* 1991; 338: 634–5.

Hepatic impairment. In a study[1] of patients with primary biliary cirrhosis the clearance of oral budesonide was significantly reduced in those with cirrhosis (stage IV) compared with milder disease (stage I/II). Elevated budesonide concentrations were sufficient to suppress cortisol production, and believed to be associated with the development of portal vein thrombosis in 2 cirrhotic patients.

1. Hempfling W, *et al.* Pharmacokinetics and pharmacodynamic action of budesonide in early- and late-stage primary biliary cirrhosis. *Hepatology* 2003; 38: 196–202.

Hypersensitivity. Contact dermatitis has been reported to topical or intranasal budesonide.[1] An anaphylactoid reaction occurred 5 minutes after the first dose of oral budesonide in a patient who had previously reacted in a similar way to mesalazine.[2]

1. Quintilliani R. Hypersensitivity and adverse reactions associated with the use of newer intranasal corticosteroids for allergic rhinitis. *Curr Ther Res* 1996; 57: 478–88.
2. Heeringa M, *et al.* Anaphylactic-like reaction associated with oral budesonide. *BMJ* 2000; 321: 927.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies budesonide as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Budesonide is rapidly and almost completely absorbed after oral administration, but has poor systemic availability (about 10%) due to extensive first-pass metabolism in the liver, mainly by the cytochrome P450 isoenzyme CYP3A4. The major metabolites, 6-β-hydroxybudesonide and 16-α-hydroxyprednisolone have less than 1% of the glucocorticoid activity of unchanged budesonide. Budesonide is reported to have a terminal half-life of about 2 to 4 hours.

General references.

1. Donnelly R, Seale JP. Clinical pharmacokinetics of inhaled budesonide. *Clin Pharmacokinet* 2001; 40: 427–40.
2. Edsbäcker S, Andersson T. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. *Clin Pharmacokinet* 2004; 43: 803–21.
3. Kraft WK, *et al.* The pharmacokinetics of nebulized nanocrystal budesonide suspension in healthy volunteers. *J Clin Pharmacol* 2004; 44: 67–72.
4. Lähelmä S, *et al.* Equivalent lung deposition of budesonide in vivo: a comparison of dry powder inhalers using a pharmacokinetic method. *Br J Clin Pharmacol* 2005; 59: 167–73.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aerovent; Aerovial; Airbude†; Budeson; Budezonil; Cuteral; Entocort; Exudrol-Bude; Hypersol B; Inflammide; Infliplus†; Nastizol Hidrospray; Neumocort; Neumotex; Proetzonide; Pulmo Lisoflam; Rino-B; Spirocort; *Austral.*: Budamax; Entocort; Pulmicort; Rhinocort; *Austria*: Budenobronch; Budiair; Budo-san; Entocort; Giona; Miflonide; Pulmicort; Rhinocort; *Belg.*: Budenofalk; Docbudeso†; Entocort; Miflonide; Pulmicort; Rhinobudesonide†; Rhinocort; *Braz.*: Budecort; Budiair; Busonid; Entocort; Miflonide; Noex; Pulmicort; *Canad.*: Entocort; Pulmicort; Rhinocort; *Chile*: Aero-Bud; Aerovial Aqua; Aerovial; Budasmal; Budenofalk; Clebudan; Inflammide; Neumocort; Pulmicort†; Rhinocort; Rino-B; *China*: Ji Shu (吉舒); Pulmicort (普米克); Rhinocort (雷诺考特); Cz.: Budenofalk; Budiair; Entocort; Giona; Miflonid; Pulmax†; Pulmicort; Rhinocort; Ribuspir†; Tafen; Tinkair; *Denm.*: Budenofalk; Endoprol†; Entocord; Entocort; Giona; Intestifalk; Miflonide; Pulmicort; Rhinocort; Rhinosol†; Spirocort; *Fin.*: Budenofalk; Entocort; Novopulmon; Pulmicort; Rhinocort; *Fr.*: Entocort; Miflonil; Mikicort; Novopulmon; Pulmicort; Rafton; Rhinocort; *Ger.*: Budapp; Budecort; Budenobronch; Budenofalk; Budes†; Budiair; Entocort; Miflonide; *Novopulmon*; Pulmax†; *Pulmicort*; *Gr.*: Abelitan; Aldesonit; Arsicort; Astrocast; Aurid; Axelovert; Beysonit; Biosonide; Budecol; Budemar; Budenite; Budenofalk; Budeprol; Buderen; Budesan; Budesoderm; Budesonal; Budiair; Busonal; Butekont; Buyamin; Dedostryl; Dexalocal; Eolan; Esonide; Etrafonil; Farlidone; Ixor†; Labetasol; Lisobron; Lydenal; Miflonide; Minalerg; Nalator; Obecirol; Obusonid; Olfo; Olfosonide; Olyspal; Pimoftal; Pulmicort; Pulmiver; Pulmovance; Resata; Rhinobros; Rhinoside; Ribuspir; Rinoster; Serbo; Sonidal; Talgan; Therasonid; Udesogel; Udesospray; Velorium; Vericort; Vernoral; Vinecort; Zefecort; Zymacter; Zyolaif; Zytual; *Hong Kong*: Budena; Budenase; Budenofalk; Butacort†; Cycortide; Entocort; Pulmicort; Rhinocort; *Hung.*: Aerox; Budenofalk; Budesogen; Entocort; Miflonide; Neplit†; Pulmax†; Pulmicort; Rhinocort; *India*: Budate; Budecort; Budenase; Budez; Budvent; Buovent DP; Derinide; Pulmicort; Rhinocort; *Indon.*: Budenofalk; Inflammide; Obucort; Pulmicort; Rhinocort; *Irl.*: Budenofalk; Budesitan; Entocort; Pulmicort; Rhinocort; *Israel*: Budeson; Budicort; Entocort; Miflonide; Nasocort; *Ital.*: Aircort; Bidien; Bodinet; Bodix; Budexan; Budiair; Budineb; Busosed; Desonax; Eltair; Entocir; Kesol; Marxide; Miflo; *Miflonide*; Pulmaxan; Rafton; Rhinocort; Spirocort; Xavin; *Malaysia*: Besonin; Budecort; Budenase; Budenide; Budiair; Butacort; Eltair; Giona; Inflammide†; Pulmicort; Rhinocort; *Mex.*: Aerosial†; Budosan†; Entocort; Miflonide; Numark; Pulmicort; Rhinocort; *Neth.*: Budenofalk; Entocort; Larbex; Pulmicort; Rhinocort; Ribuspir†; *Norw.*: Entocort; Giona; Pulmicort; Rhinocort; *NZ*: Budenocort; Butacort; Eltair; Entocort; Pulmicort; *Philipp.*: Asmavent; Bronex; Budecort; Budenofalk; Denecort; Obucort; Primavent; *Pol.*: Budenofalk; Buderhin; Budiair; Entocort; Horacort†; Miflonide; Neplit; Pulmicort; Rhinocort; Tafen; *Port.*: Aeromax; Budiair; Budo-san; Entocort; Miflonide; Neo Rinactive†; Pulmax†; Pulmicort; *Rus.*: Benacort (Бенакорт); Benarin (Бенарин); Budenofalk (Буденофальк); Budiair (Будиэйр); Cycortide (Цикортид); Pulmicort (Пульмикорт); Tafen (Тафен); *S.Afr.*: Budeflam; Entocord; Inflammide; Inflanaze; Pulmicort; Rhinocort; *Singapore*: Budenofalk; Eltair; Esonide; Frenolyn; Giona; Inflammide†; Pulmicort; Rhinocort; *Spain*: Budena†; Demotest†; Entocord; Intestifalk; Miflonide; Neo Rinactive†; Novopulm; Olfex; Pulmicort; Pulmictan; Rhinocort; Ribujet; *Swed.*: Budenofalk; Desonix; Entocort; Giona; Novopulmon; Pulmicort; Rhinocort; *Switz.*: Budenid; Budenofalk; Cortinasal; Entocort; Miflonide; Pulmicort; Rhinocort; *Thai.*: Aeronide; Besonin; Budecort; BudeSpray; Budiair; Bunase; Eltair†; Giona; Obucort; Pulmicort; Rhinocort; *Turk.*: Budenofalk; Budiair; Entocort; Giona; Inflacort; Miflonide; Neo Rinactive; Neo-Rinactive; Pulmicort; Rhinocort; *UAE*: Sonidar; *UK*: Budelin; Budenofalk; Entocort; Pulmicort; Rhinocort; *Ukr.*: Budenofalk (Буденофальк); Novopulmon (Новопульмон); Pulmicort (Пульмикорт); Tafen (Тафен); *USA*: Entocort; Pulmicort; Rhinocort; Uceris; *Venez.*: Biosonida; Bronklast; Budecort; Budenas; Miflonide; Pulmicort; Pulmolet; Rhinocort; Rinolet.

Multi-ingredient Preparations. *Arg.*: Frevia; Neumoterol; Symbicort; *Austral.*: Symbicort; *Austria*: Symbicort; *Belg.*: Symbicort; *Braz.*: Alenia; Foraseq; Symbicort; Vannair; *Canad.*: Symbicort; *Chile*: Symbicort; Vannair; *China*: Symbicort (信必可); *Cz.*: Budfor; Edoflo; Symbicort; *Denm.*: Assieme; Rilast; Sinestic Symbicort; *Fin.*: Symbicort; *Fr.*: Symbicort; *Ger.*: Symbicort; *Gr.*: Symbicort; *Hong Kong*: Symbicort; *Hung.*: Symbicort; *India*: Budamate; Budesal; Fomtide; Foracort; Formonide; *Indon.*: Symbicort; *Irl.*: Budfor; Edoflo; Symbicort; *Israel*: Symbicort; *Ital.*: Assieme; Assiememite; Sinestic; Sinesticmite†; Symbicort; *Jpn*: Symbicort; *Malaysia*: Foracort; Symbicort; *Mex.*: Symbicort; *Neth.*: Assieme; Budfor; Edoflo†; Sinestic Symbicort; *Norw.*: Symbicort; *NZ*: Symbicort; Vannair; *Philipp.*: Symbicort; *Pol.*: Symbicort; *Port.*: Assieme; Symbicort; *Rus.*: Biasten (Биастен); Foradil Combi (Форадил Комби); Simbicort (Симбикорт)†; Symbicort (Симбикорт); *S.Afr.*: Symbicord; *Singapore*: Symbicort; *Spain*: Rilast; Symbicort; *Swed.* Symbicort; *Switz.*: Symbicort; Vannair; *Thai.*: Symbicon *Turk.*: Combipack; Foradil Combi; Symbicort; Ventofor-Combi *UK*: Symbicort; *Ukr.*: Simbicort (Симбикорт); *USA*: Symbicort *Venez.*: Foraseq; Symbicort.

Pharmacopoeial Preparations

BP 2014: Budesonide Aqueous Nasal Spray; Budesonid Inhalation Powder, pre-dispensed; Budesonide Inhalatio Powder; Budesonide Nebuliser Suspension; Budesonide Pres surised Inhalation.

Ciclesonide (USAN, rINN) ⊗

BY-9010; Ciclesonida; Ciclésonide; Ciclesonidum; RPR 251526; Циклезонид.

(*R*)-11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate.

$C_{32}H_{44}O_7$=540.7

CAS — 126544-47-6; 141845-82-1.

ATC — R01AD13; R03BA08.

ATC Vet — QR01AD13; QR03BA08.

UNII — S59502I185.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ciclesonide). A white or yellowish-white crystalline powder. Practically insoluble in water; freely soluble to soluble in acetone and in dehydrated alcohol.

Uses and Administration

Ciclesonide is a corticosteroid with glucocorticoid activity (p. 1597.1). It is used by inhalation in the management of **asthma** (see p. 1627.1). The usual dose is 160 micrograms daily from a metered-dose aerosol, given either once daily or in 2 divided doses. In severe asthma, a dose of 320 micrograms twice daily may be used. The dose may be reduced to 80 micrograms once daily for maintenance. Ciclesonide is given intranasally for the treatment of

Tosactide is another polypeptide analogue of corticotropin; it has the same sequence as the first 28 residues.

Corticotropin has been available for injection in two forms. One form is a plain injection that may be given by the subcutaneous, intramuscular, or intravenous routes. The other form is a long-acting depot preparation in which the viscosity is increased by the addition of gelatin, and which is given subcutaneously or intramuscularly; it must not be given intravenously. Individual responses to therapeutic corticotropin vary considerably and doses must be adjusted accordingly.

For *diagnostic purposes* the corticotropin test is based on the measurement of plasma-cortisol concentrations before and after injection. The plain preparation is used in doses of 10 to 25 units in 500 mL of glucose 5% infused intravenously over 8 hours.

For *therapeutic purposes* typical doses for the depot preparation have been about 40 to 80 units every 24 to 72 hours by the subcutaneous or the intramuscular route. As soon as possible the dosage should be reduced gradually to the minimum necessary to control symptoms.

A depot preparation of corticotropin combined with zinc hydroxide for intramuscular injection has been used in the past.

Epilepsy. The use of corticotropin in the management of infantile spasms is referred to under Epilepsy in Corticosteroids, p. 1604.1.

Multiple sclerosis. Short-term courses of corticotropin have been used to speed recovery from acute exacerbations of multiple sclerosis (p. 996.3) but corticosteroids, usually methylprednisolone, are now preferred.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or tetracosactide, but a controlled study of tetracosactide use found no benefit (see p. 1648.2).

Adverse Effects

Corticotropin stimulates the adrenals to produce cortisol (hydrocortisone) and mineralocorticoids; it therefore has the potential to produce similar adverse glucocorticoid and mineralocorticoid effects to those of the corticosteroids (see p. 1615.3). In particular, its mineralocorticoid properties can produce marked sodium and water retention; considerable potassium loss may also occur.

Corticotropin can induce sensitisation, and severe hypersensitivity reactions, including anaphylaxis, may occur. This is generally considered to be due to the porcine component of the peptide.

Whereas corticosteroids replace endogenous cortisol (hydrocortisone) and thereby induce adrenal atrophy, corticotropin's stimulant effect induces hypertrophy. Nevertheless, the ability of the hypothalamic-pituitary-adrenal axis to respond to stress is still reduced, and abrupt withdrawal of corticotropin may result in symptoms of adrenal insufficiency (see Withdrawal, below).

Reports of adverse effects in children given corticotropin for infantile spasms.

1. Riikonen R, Donner M. ACTH therapy in infantile spasms: side effects. *Arch Dis Child* 1980; 55: 664–72.
2. Hanefeld F, *et al.* Renal and pancreatic calcification during treatment of infantile spasms with ACTH. *Lancet* 1984; i: 901.
3. Riikonen R, *et al.* Disturbed calcium and phosphate homeostasis during treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; 61: 671–6.
4. Perheentupa J, *et al.* Adrenocortical hyporesponsiveness after treatment with ACTH of infantile spasms. *Arch Dis Child* 1986; 61: 750–3.

Withdrawal

Corticotropin use may depress the hypothalamic-pituitary-adrenal axis. Abrupt withdrawal of corticotropin may therefore produce adrenocortical and pituitary unresponsiveness, and therapy should be stopped gradually. An increase in corticosteroid requirements associated with the stress of infection, or accidental or surgical trauma, may also precipitate acute adrenocortical insufficiency. See also Withdrawal under Corticosteroids, p. 1618.1.

Precautions

As for Corticosteroids, p. 1618.3.

Phaeochromocytoma. A hypertensive crisis in a patient given intravenous tetracosactide led to the discovery of an adrenaline-secreting phaeochromocytoma.[1] It was suggested that corticotropin should be used with caution in patients with orthostatic hypotension in whom the diagnosis of phaeochromocytoma has not been excluded.

1. Jan T, *et al.* Epinephrine-producing pheochromocytoma with hypertensive crisis after corticotropin injection. *Am J Med* 1990; 89: 824–5.

Interactions

Interactions seen with corticotropin are liable to be similar to those with corticosteroids (p. 1619.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acthelea; *India*: Acton Prolongatum; *USA*: Acthar.

Pharmacopoeial Preparations
USP 36: Corticotropin for Injection; Corticotropin Injection; Corticotropin Zinc Hydroxide Injectable Suspension; Repository Corticotropin Injection.

Cortisone Acetate *(BANM, rINNM)* ⊗

Acetato de cortisona; Compound E Acetate; Cortisona, acetato de; Cortisonacetat; Cortisone, Acétate de; Cortisoni Acetas; 11-Dehydro-17-hydroxycorticosterone Acetate; Kortisonacetat; Kortison-acetát; Kortisoniasetaatti; Kortizon-acetát; Kortizono acetatas; Kortyzonu octan; Кортизона Ацетат.

17α,21-Dihydroxypregn-4-ene-3,11,20-trione 21-acetate.

$C_{23}H_{30}O_6$=402.5

CAS — 53-06-5 (cortisone); 50-04-4 (cortisone acetate).

ATC — H02AB10; S01BA03.

ATC Vet — QH02AB10; QS01BA03.

UNII — 883WKN7W8X.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Cortisone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; freely soluble in dichloromethane; soluble in dioxan. Protect from light.

USP 36: (Cortisone Acetate). A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 350 of alcohol, 1 in 75 of acetone, 1 in 4 of chloroform, and 1 in 30 of dioxan. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Uses and Administration

Cortisone is a corticosteroid secreted by the adrenal cortex. It has glucocorticoid activity (p. 1597.1), as well as appreciable mineralocorticoid activity; 25 mg of cortisone acetate is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

Cortisone acetate is rapidly effective when given orally, and more slowly by intramuscular injection.

Cortisone acetate has been used mainly for replacement therapy in adrenocortical insufficiency (p. 1600.2), but hydrocortisone (p. 1640.1) is generally preferred since cortisone itself is inactive and must be converted by the liver to hydrocortisone, its active metabolite; hence, in some liver disorders the activity of cortisone may be less reliable. Doses of cortisone acetate for oral replacement therapy are 12.5 to 37.5 mg daily in divided doses, with fludrocortisone if additional mineralocorticoid activity is required.

Cortisone acetate has been used in the treatment of many of the allergic and inflammatory disorders for which corticosteroid therapy is helpful (p. 1597.3) but prednisolone or other synthetic glucocorticoids are generally preferred. Oral doses of cortisone acetate have generally ranged from about 25 to 300 mg daily. It has also been given by intramuscular injection.

Homoeopathy

Cortisone has been used in homoeopathic medicines.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Cortisone acetate is readily absorbed from the gastrointestinal tract and the cortisone is rapidly converted in the liver to its active metabolite, hydrocortisone (cortisol). The biological half-life of cortisone itself is only about 30 minutes. Absorption of cortisone acetate from intramuscular sites is considerably slower than after oral doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Cortate; *Ital.*: Cortone; *UK*: Cortisyl; *USA*: Cortone†.

Multi-ingredient Preparations. *Braz.*: Corciclen; *Spain*: Blefarida†; Gingilone.

Homoeopathic Preparations. *Ger.*: Cortirell†; Cortisorell; *Neth.*: Pulsatilla comp.

Pharmacopoeial Preparations
BP 2014: Cortisone Tablets;
USP 36: Cortisone Acetate Injectable Suspension; Cortisone Acetate Tablets.

Cortivazol *(USAN, pINN)* ⊗

Cortivazolum; H-3625; MK-650; NSC-80998; Кортивазол.

11β,17α,21-Trihydroxy-6,16α-dimethyl-2′-phenyl-2′*H*-pregna-2,4,6-trieno[3,2-*c*]pyrazol-20-one 21-acetate.

$C_{32}H_{38}N_2O_5$=530.7

CAS — 1110-40-3.

ATC — H02AB17.

ATC Vet — QH02AB17.

UNII — YM183K0H63.

Profile

Cortivazol is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 300 micrograms of cortivazol is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is given in the treatment of musculoskeletal and joint disorders by intra-articular, periarticular, or epidural injection in doses of about 1.25 to 3.75 mg, according to the size of the joint, usually at intervals of 1 to 3 weeks. It has also been given orally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Altim; *Gr.*: Altim.

Deflazacort *(BAN, USAN, rINN)* ⊗

Azacort; Deflatsakorti; Deflazacort; Deflazacortum; Deflazakort; DL-458-IT; L-5458; MDL-458; Oxazacort; Дефлазакорт.

11β,21-Dihydroxy-2′-methyl-5′β*H*-pregna-1,4-dieno[17,16-*d*]oxazole-3,20-dione 21-acetate.

$C_{25}H_{31}NO_6$=441.5

CAS — 14484-47-0.

ATC — H02AB13.

ATC Vet — QH02AB13.

UNII — KR5YZ6AE4B.

Profile

Deflazacort is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 6 mg of deflazacort is reportedly equivalent in anti-inflammatory activity to about 5 mg of prednisolone (but see Action, below).

Deflazacort is used for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy (p. 1597.3). It is given in initial oral doses of up to 120 mg daily; usual maintenance doses are 3 to 18 mg daily. For doses used in children, see p. 1630.1.

References.

1. Markham A, Bryson HM. Deflazacort: a review of its pharmacological properties and therapeutic efficacy. *Drugs* 1995; 50: 317–33.
2. Mignogna MD, *et al.* Oral pemphigus: long term behaviour and clinical response to treatment with deflazacort in sixteen cases. *J Oral Pathol Med* 2000; 29: 145–52.
3. Campbell C, Jacob P. Deflazacort for the treatment of Duchenne dystrophy: a systematic review. *BMC Neurol* 2003; 3: 7. Available at: http://www.biomedcentral.com/1471-2377/3/7 (accessed 20/06/06)
4. Biggar WD, *et al.* Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. *Neuromuscul Disord* 2006; 16: 249–55.

Action. Although it has been suggested that deflazacort produces fewer adverse effects than some conventional corticosteroids such as prednisolone, a study in healthy subjects found that the ratio of efficacy for deflazacort compared with prednisolone was higher than the 1.2:1 previously assumed,[1] implying that lower effective doses of deflazacort had been used in such comparisons. A review[2] of clinical studies of patients treated with deflazacort concluded that it was slightly less potent than prednisolone, and that many of the data on adverse effects

were inconsistent. All systemic corticosteroids may produce clinically significant adverse reactions (see also p. 1615.3), which are mainly dependent on dose and duration of use.

1. Babadjanova G, *et al.* Comparison of the pharmacodynamic effects of deflazacort and prednisolone in healthy subjects. *Eur J Clin Pharmacol* 1996; 51: 53–7.
2. Anonymous. Deflazacort – an alternative to prednisolone? *Drug Ther Bull* 1999; 37: 57–8.

Administration in children. Deflazacort is used in children for its anti-inflammatory and immunosuppressant properties in conditions responsive to corticosteroid therapy. Oral doses of 0.25 to 1.5 mg/kg daily may be used. The *BNFC* suggests that this dose may be given once daily or on alternate days in children aged from 1 month up to 12 years, and states that up to 2.4 mg/kg (to a maximum of 120 mg) daily has been used in emergency situations. Older children may be given adult doses (see p. 1629.3).

Renal calculi. Deflazacort has been given with nifedipine to ease the spontaneous passage of renal calculi and stone fragments (see under Nifedipine, p. 1450.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Azacortid; Cordefla; Defas; Flamirex; *Braz.*: Calcort; Cortax; Deflaimmun; Deflanil; Denacen; Flaz-Cort; Flazal; *Chile*: Azacortid; Dezartal; *Ger.*: Calcort; *Gr.*: Deflan; Flantadin; *India*: Alnacort; Cincort; Core; Cortimax; Defcort; Defglu; Defjee; Deflar; Defocart; Defza; Dezert; DFZ; Ducort; Emzacort; Flazlar; Flozamin; Flozastar; Laza; Lazoc; MDCort; Medipred; MP Next; Nayacort; New Premisol; Nuradef; *Irl.*: Calcort†; *Ital.*: Deflan; Flantadin; *Mex.*: Calcort; Carzoflep; Setatrep; *Port.*: Desay; Rosilan; *Spain*: Dezacor; Zamene; *Switz.*: Calcort; *Turk.*: Flantadin; *UK*: Calcort; *Venez.*: Calcort.

Deprodone *(BAN, rINN)* ⊗

Deprodona; Déprodone; Deprodonum; Desolone; RD-20000 (deprodone propionate); Депродон.

11β,17α-Dihydroxypregna-1,4-diene-3,20-dione.

$C_{21}H_{28}O_4$=344.5

CAS — 20423-99-8 (deprodone); 20424-00-4 (deprodone propionate).

UNII — Z380L7N00P.

NOTE. The names Allomidon and Eclar have been used as trade marks for deprodone propionate.

Profile

Deprodone is a corticosteroid that has been used topically as the propionate.

Desonide *(BAN, USAN, rINN)* ⊗

D-2083; Desfluorotriamcinolone Acetonide; Desonid; Desonida; Désonide; Desonidi; Desonidum; 16-Hydroxyprednisolone 16,17-Acetonide; Prednacinolone Acetonide; Дезонид.

11β,21-Dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{32}O_6$=416.5

CAS — 638-94-8.

ATC — D07AB08; S01BA11.

ATC Vet — QD07AB08; QS01BA11.

UNII — J280872D1O.

Profile

Desonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, ointment, lotion, gel, or foam containing 0.05%. The pivalate ester has also been used.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Desonide sodium phosphate has been used in preparations for ocular use.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desonide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Desoplus; DesOwen; Locatop; *Austral.*: DesOwen; *Braz.*: Dermatol; Desonol; *Canad.*: Desocort; Tridesilon; Verdeso; *Chile*: DesOwen; *China*: DesOwen (莱索文); Li Yan Zhuo (力言卓); *Cz.*: Locatop†; *Fin.*: Apolar; *Fr.*: Locapred; Locatop; Tridesonit; *Hong Kong*: DesOwen; *India*: DesOwen; *Indon.*: Apolar; Dermades; Dermanide; Desolex; Nufapolar; *Israel*: Locatop; *Ital.*: Prenacid; Reticus; Sterades; *Mex.*: Dersupril; DesOwen; *Norw.*: Apolar; *Philipp.*: DesOwen; *Pol.*: Locatop; *Port.*: Locapred†; Zotinar; *Rus.*: Prenacid (Пренацид); *Singapore*: DesOwen; *Switz.*: Locapred; Locatop†; *Turk.*: Prenacid; *USA*: Desonate; DesOwen; LoKara†; Verdeso; *Venez.*: Dermosupril; DesOwen; Erilon.

Multi-ingredient Preparations. *Fr.*: Cirkan a la Prednacinolone; *Indon.*: Apolar-N; Desolex-N; *Norw.*: Apolar med dekvalin; *Port.*: Zotinar-N; *Venez.*: Dermosupril C.

Desoximetasone *(BAN, USAN, rINN)* ⊗

A-41-304; Desoksimetasoni; Desoximetason; Desoximetasona; Désoximéthasone; Desoximetasonum; Desoxymethasone; Hoe-304; R-2113; Дезоксиметазон.

9α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 382-67-2.

ATC — D07AC03.

ATC Vet — QD07AC03; QD07XC02.

UNII — 4E07GX87AU.

Pharmacopoeias. In *US*.

USP 36: (Desoximetasone). A white to practically white, odourless, crystalline powder. Insoluble in water; freely soluble in alcohol, in acetone, and in chloroform.

Profile

Desoximetasone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, or ointment; concentrations used range from 0.05 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Adverse effects. A photosensitivity reaction occurred in a patient treated for psoriasis with topical desoximetasone; rechallenge led to a recurrence.[1] The patient was also receiving propranolol hydrochloride.

1. Stierstorfer MB, Baughman RD. Photosensitivity to desoximetasone emollient cream. *Arch Dermatol* 1988; 124: 1870–1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies desoximetasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Esperson; *Canad.*: Desoxi; Topicort; *Denm.*: Ibaril†; *Fin.*: Ibaril; *Ger.*: Topisolon; *Indon.*: Dercason; Desomex†; Dexigen; Dexocort; Dexosyn; Esperson; Inerson; Lerskin; Pyderma; Soderma†; Topcort; *Ital.*: Flubason; *Neth.*: Ibaril; Topicorte; *Norw.*: Ibaril; *Spain*: Flubason; *Switz.*: Topisolon†; *Thai.*: Cendexsone†; Esperson; TO Corte; Topicorte; Topoxy; *USA*: Topicort.

Multi-ingredient Preparations. *Braz.*: Esperson N; *Indon.*: Denomix; *Thai.*: Topifram.

Pharmacopoeial Preparations

USP 36: Desoximetasone Cream; Desoximetasone Gel; Desoximetasone Ointment.

Desoxycortone *(BAN, rINN)*

Decortone; Deoxycortone; Desoksikortoni; Desoxicortona; Desoxikorton; Desoxycorticosterone; Désoxycortone; Desoxycortonum; Дезоксикортон.

21-Hydroxypregn-4-ene-3,20-dione.

$C_{21}H_{30}O_2$=314.5

CAS — 64-85-7.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 40GP3SYQ49.

Desoxycortone Acetate *(BANM, rINNM)*

Acetato de desoxicortona; Cortin; Decortone Acetate; 11-Deoxycorticosterone Acetate; Deoxycortone Acetate; Desoksikortoniasetaatti; Desoxicortona, acetato de; Desoxikortonacetat; Desoxycorticosterone Acetate; Desoxycortonacetat; Désoxycortone, acétate de; Desoxycortoni Acetas; Desoxykorton-acetát; Dezoksikortono acetatas; Dezoksykortonu octan; Dezoxikorton-acetát; Дезоксикортона Ацетат.

Desoxycortone 21-acetate.

$C_{23}H_{32}O_4$=372.5

CAS — 56-47-3.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 6E0A168O88.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Desoxycortone Acetate). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water; sparingly soluble in alcohol; soluble in acetone; freely soluble in dichloromethane; slightly soluble in propylene glycol and in fatty oils. Protect from light.

USP 36: (Desoxycorticosterone Acetate). A white or creamy-white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, and in dioxan; slightly soluble in vegetable oils. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Desoxycortone Pivalate *(BANM, rINNM)*

Deoxycorticosterone Pivalate; Deoxycorticosterone Trimethylacetate; Deoxycortone Pivalate; Deoxycortone Trimethylacetate; Desoxicortona, pivalato de; Desoxycorticosterone Pivalate; Desoxycorticosterone Trimethylacetate; Désoxycortone, Pivalate de; Desoxycortoni Pivalas; Pivalate de desoxicortona; Дезоксикортона Пивалат.

Desoxycortone 21-pivalate.

$C_{26}H_{38}O_4$=414.6

CAS — 808-48-0.

ATC — H02AA03.

ATC Vet — QH02AA03.

UNII — 16665T4A2X.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Desoxycorticosterone Pivalate). Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Profile

Desoxycortone is a corticosteroid secreted by the adrenal cortex and has mainly mineralocorticoid activity (p. 1597.1). It has no significant glucocorticoid action.

Desoxycortone acetate has been used in the treatment of adrenocortical insufficiency (p. 1600.2) as an adjunct to cortisone or hydrocortisone. For this purpose, however, fludrocortisone given orally is now usually preferred.

Desoxycortone acetate is given by intramuscular injection as an oily solution, in doses of up to 10 mg once or twice daily.

Desoxycortone has also been used as its enantate, phenylpropionate, and sodium hemisuccinate esters. Desoxycortone pivalate is used in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Syncortyl; *Ital.*: Cortiron.

Multi-ingredient Preparations. *Gr.*: Docabolin†.

Pharmacopoeial Preparations

USP 36: Desoxycorticosterone Acetate Injection; Desoxycorticosterone Acetate Pellets.

Dexamethasone *(BAN, rINN)* ⊗

Deksametasoni; Deksametazon; Deksametazonas; Dexamethasone; Dexametason; Dexametasona; Dexametasone; Dexametazon; Dexaméthasone; Dexamethasonum; 9α-Fluoro-16α-methylprednisolone; Hexadecadrol; Дексаметазон.

9α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_5$=392.5

CAS — 50-02-2.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

seasonal and perennial allergic **rhinitis** (p. 612.1) in adults and adolescents 12 years of age and older; children 6 years of age and older may be treated for seasonal allergic rhinitis. A dose of 200 micrograms once daily is given as 2 sprays of 50 micrograms into each nostril.

Administration in children. Ciclesonide may be given intranasally for the treatment of seasonal allergic rhinitis in children aged 6 years and older, in the same dose used in adults (see p. 1626.3).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Reviews of ciclesonide.

1. Deeks ED, Perry CM. Ciclesonide: a review of its use in the management of asthma. *Drugs* 2008; 68: 1741–70.
2. Manning P, *et al.* Ciclesonide versus placebo for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 10/03/10).
3. Manning P, *et al.* Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2008 (accessed 10/03/10).

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1.

Reviews of ciclesonide.

1. Dhillon S, Wagstaff AJ. Ciclesonide nasal spray: in allergic rhinitis. *Drugs* 2008; 68: 875–83.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Systemic absorption may follow inhalation of ciclesonide, particularly if high doses are used for prolonged periods.

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Ciclesonide is hydrolysed to its biologically active metabolite, desciclesonide, by esterase enzymes in the lung and nasal mucosa. The systemic bioavailability for desciclesonide is reported to be more than 50% when ciclesonide is given by metered-dose inhaler; desciclesonide has also been found in the serum of some patients after nasal use. Oral bioavailability is less than 1%. Ciclesonide and desciclesonide are extensively bound to plasma proteins. It is further metabolised to inactive metabolites mainly via the cytochrome P450 isoenzyme CYP3A4, and to a lesser extent by CYP2D6. The mean elimination half-life of desciclesonide is about 6 to 7 hours after inhalation of ciclesonide. After oral or intravenous dosage, ciclesonide is mainly excreted via the faeces.

Reviews.

1. Derendorf H. Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. *J Clin Pharmacol* 2007; 47: 782–9.
2. Nave R. Clinical pharmacokinetic and pharmacodynamic profile of inhaled ciclesonide. *Clin Pharmacokinet* 2009; 48: 243–52.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alvesco; Cicletex; Omnaris; ***Austral.***: Alvesco; Omnaris; ***Austria***: Alvesco; ***Belg.***: Alvesco; ***Braz.***: Alvesco; Omnaris; ***Canad.***: Alvesco; Omnaris; ***Chile***: Alvesco†; ***Cz.***: Alvesco; ***Denm.***: Alvesco; ***Fin.***: Alvesco; ***Fr.***: Alvesco; ***Ger.***: Alvesco; ***Gr.***: Alvesco; Amavio; Freathe; ***Hong Kong***: Alvesco; Omnaris; ***Hung.***: Alvesco; ***India***: Ciclohale; Osonide†; ***Irl.***: Alvesco; ***Israel***: Alvesco; ***Jpn***: Alvesco; ***Malaysia***: Alvesco; Omnaris; ***Mex.***: Alvesco; Omnaris; ***Neth.***: Alvesco; ***Norw.***: Alvesco; ***Philipp.***: Omnaris; ***Pol.***: Alvesco; ***Port.***: Alvesco; ***S.Afr.***: Alvesco; ***Singapore***: Alvesco; ***Spain***: Alvesco; ***Swed.***: Alvesco; ***Switz.***: Alvesco; ***Turk.***: Alvesco; ***UK***: Alvesco; ***USA***: Alvesco; Omnaris; Zetonna; ***Venez.***: Alvesco.

Clobetasol Propionate *(BANM, USAN, rINNM)* ⊗

CCI-4725; Clobétasol Propionate de; Clobetasol, propionato de; Clobetasoli Propionas; Clobetasolpropionat; GR-2/925; Klobetasol-propionát; Klobetazol Propionat; Klobetazolu propionian; Propionato de clobetasol; Клобетазона Пропионат.

21-Chloro-9α-fluoro-11β,17α-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

$C_{25}H_{32}ClFO_5$=467.0

CAS — 25122-41-2 (clobetasol); 25122-46-7 (clobetasol propionate).

ATC — D07AD01.

ATC Vet — QD07AD01.

UNII — 779619577M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Clobetasol Propionate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone. Protect from light.

USP 36: (Clobetasol Propionate). A white to cream crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; soluble in acetone, in chloroform, in dimethyl sulfoxide, in dioxan, and in methyl alcohol; slightly soluble in benzene and in ether. Store in airtight containers. Protect from light.

Profile

Clobetasol propionate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, ointment, gel, scalp application, shampoo, or foam containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Clobetasol butyrate has also been used similarly.

References.

1. Campisi G, *et al.* A new delivery system of clobetasol-17-propionate (lipid-loaded microspheres 0.025%) compared with a conventional formulation (lipophilic ointment in a hydrophilic phase 0.025%) in topical treatment of atrophic/erosive oral lichen planus: a phase IV, randomized, observer-blinded, parallel group clinical trial. *Br J Dermatol* 2004; 150: 984–90.
2. Jarratt M, *et al.* Clobetasol propionate shampoo 0.05%: a new option to treat patients with moderate to severe scalp psoriasis. *J Drugs Dermatol* 2004; 3: 367–73.
3. Reygagne P, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; 16: 31–6.
4. Breneman D, *et al.* Clobetasol propionate 0.05% lotion in the treatment of moderate to severe atopic dermatitis: a randomized evaluation versus clobetasol propionate emollient cream. *J Drugs Dermatol* 2005; 4: 330–6.
5. Lowe N, *et al.* Clobetasol propionate lotion, an efficient and safe alternative to clobetasol propionate emollient cream in subjects with moderate to severe plaque-type psoriasis. *J Dermatol Treat* 2005; 16: 158–64.
6. Reid DC, Kimball AB. Clobetasol propionate foam in the treatment of psoriasis. *Expert Opin Pharmacother* 2005; 6: 1735–40.
7. Sanchez Regana M, *et al.* Treatment of nail psoriasis with 8% clobetasol nail lacquer: positive experience in 10 patients. *J Eur Acad Dermatol Venereol* 2005; 19: 573–7.
8. Conrotto D, *et al.* Ciclosporin vs. clobetasol in the topical management of atrophic and erosive oral lichen planus: a double-blind, randomized controlled trial. *Br J Dermatol* 2006; 154: 139–45.
9. Vena GA, *et al.* Clobetasol propionate 0.05% in a novel foam formulation is safe and effective in the short-term treatment of patients with delayed pressure urticaria: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006; 154: 353–6.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clobetasol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Clob-X; Clobefar; Clobesol; Dermaclob; Dermadex; Dermexane Capilar; Dermexane; Perfracort; Ribatra; Salac; ***Austria***: Clarelux; Clobex; Dermovate; ***Belg.***: Clarelux; Clobex; Dermovate; ***Braz.***: Clob-X; Clobesol; Cortalen C; Dermacare; Propiosol; Psorex; Psorin†; Therapsor; ***Canad.***: Clobex; Dermovate; ***Chile***: Alticort†; Balsan; Clob-X; Clodavan; Cortopic†; Dermovate; Koniderm; Xinder; ***China***: Dermovate (特美夫); En Fu Shuang (恩肤霜); Eurobetsol (欧博士); Xian Ke Xin (显克欣); ***Cz.***: Clobex; Clovate; Dermovate; Hoziac†; ***Denm.***: Clobex; Dermovat; ***Fin.***: Clarelux; Clobex; Dermovat; ***Fr.***: Clarelux; Clobex; Dermoval; ***Ger.***: Clarelux; Clobegalen; Clobex; Dermoxin; Dermoxinale; Karison; ***Gr.***: Butavate; Clarelux; Clobex; Rubocord; Yugofin; ***Hong Kong***: Clobasol; Clobesol; Clobetaderm†; Clobex; Cloderm; Dermo†; Dermovate; Dermowel†; Dhabesol; Eurobetsol; Medodermone; Uni-Dermo†; Uniderm; Univatet†; ***Hung.***: Clobex; Closanasol; Dermovate; ***India***: Betanate; Clobaderm; Clobetamil; Clobetavate; Cloderm; Clodip; Clofoam; Clomic; Clonate; Clop-E; Clop; Clorap; Cortaz; Cortisol; Cosvate; Cotrimax; Cutivate; Dermotyl; Diplene-AF; Ecziclo; Enderm; Eumosone; Excel; Kloryl; Lobate; Lobesol; Magclo; Tenovate; Topifort; ***Indon.***: Bersol; Clobesan; Clofalam; Cloflam; Clonaderm; Closol†; Dermovate; Elopro; Forderm; Hercum; Ikaderm; Kloderma; Klonat†; Lamodex; Lotasbat; Primaderm†; Psoriderm; Tempovate; ***Irl.***: Clarelux; Dermovate; Etrivex; ***Israel***: Dermovate; ***Ital.***: Clobesol; Olux; ***Malaysia***: Clobet; Clobex; Cloderm; Dermosol; Dermovate; Dhabesol; Uniderm; Univate; ***Mex.***: Clobesol; Clobexpro; Clobixfoam; Dermatovate; Lobevat; ***Neth.***: Clarelux; Clobex; Dermovate; ***Norw.***: Clobex; Dermovat; ***NZ***: Clobex; Dermol; ***Philipp.***: Cleovate; Clobex; Clobison; Clonate; Closderm; Dermosol; Dermovate; Burobel; Glevate; Probelin; ***Pol.***: Clobederm; Clobex; Dermiklobal; Dermovate; Novate; ***Port.***: Clarelux; Dermovate; Etrivex; ***Rus.***: Clovate (Кловейт); Dermovate (Дермовейт); Powercort (Пауэркорт); ***S.Afr.***: Clobex; Dermovate; Dovate; Xenovate; ***Singapore***: Clobex; Cloderm; Clonovate; Dermosol; Dermovate; Dhabesol; Lobesol; Medodermone; Powercort; SP-Clobesol; Steriderm-S; Uniderm; Univate; ***Spain***: Clarelux; Clobex; Clovate; Decloban; ***Swed.***: Clobex; Dermovat; ***Switz.***: Clarelux; Clobex; Dermovate; ***Thai.***: Betasol; Chinovate; Clinoderm; Clobasone; Clobet; Clobetate; Clobex; Cloderm; Clodermis; Clonovate; Clotasol; Cobesol; Cotaso; Delacor; Dergemate; Dermaman; Dermovate; Kaltazone; Klobecort; P-Vate; Selma; Stivate; Tacosol; Uniderm; ***Turk.***: Dermovate; Psoderm; Psovate; ***UAE***: Gamavate; ***UK***: Clarelux; ClobaDerm; Dermovate; Etrivex; ***Ukr.***: Clovate (Кловейт); Delor (Делор); Dermovate (Дермовейт); ***USA***: Clobex; Cormax; Olux; Temovate; ***Venez.***: Dermovate.

Multi-ingredient Preparations. ***Arg.***: Clobeplus; Clobesol LA; Dermadex NN; Dermexane; ***China***: Baolongkang (保龙康); Compound Ketoconazole (复方酮康唑); Dapule (达普乐); Jin Niu Er (金纽尔); ***Hong Kong***: Clobert-G†; Clonetin†; Neoclobet†; Uni-Quaderm†; ***India***: Alclos-GM; Betalic; Betanate G; Betanate GM; Betanate M; Betaspi-GM; CGM; Clobact-GM; Clobaderm-GM; Clobasia-GM; Clobecos-GM; Cloberis-GM; Clobesym-GM; Clobeta-CP; Clobetamil-G; Clobquad; Cloby; Cloderm-GM; Clodip-GM; Clogem; Clogem; Clomic-M; Clomic-S; Clomic-ZM; Clonate-F; Clonate-G; Clonate-GM; Clop-G; Clop-M; Clop-MG; Clop-S; Clorap-S; Clos-GM; Clotof-G; Clotof-GM; Clotof-M; Cortaz-S; Cortisol-G; Cosvate-G; Cosvate-GM; Cutasol-GM; Cutivate-GT; Cutivate-MF; Cutivate-S; Dermocrat Plus; Dermonit; Dermotel; Dermotriad; Dermotyl-M; Dipgenta Plus; Dipsalic-F; Ecziclo-G; Ecziclo-GM; Ecziclo-M; Enderm-GM; Etan-G; Etan-GM; Excel-M; Fungifite; Hyton; Kloryl-G; Kloryl-M; Labosol-GM; Leobet-GZ; Leta-GM; Lobate-G; Lobate-GM; Lobate-GN; Lobate-M; Lobate-S; Magclo-G; Miclogenta; Micogram; Nadicin-C; Nadoxin-C; Tenovate G; Tenovate M; ***Philipp.***: Dermovate-NN; ***UK***: Dermovate-NN†.

Pharmacopoeial Preparations

BP 2014: Clobetasol Cream; Clobetasol Ointment;
USP 36: Clobetasol Propionate Cream; Clobetasol Propionate Ointment; Clobetasol Propionate Topical Solution.

Clobetasone Butyrate *(BANM, USAN, rINNM)* ⊗

Butirato de clobetasona; CCI-5537; Clobetasona, butirato de; Clobetasonbutyrat; Clobétasone, Butyrate de; Clobetasoni Butiras; Clobetasoni Butyras; GR-2/1214; Klobetasonbutyrat; Klobetason-butyrát; Klobetasonibutyraatti; Klobetazon Bütirat; Klobetazon-bütirát; Klobetazono butiratas; Клобетазона Бутират.

21-Chloro-9α-fluoro-17α-hydroxy-16β-methylpregna-1,4-diene-3,11,20-trione 17-butyrate.

$C_{26}H_{32}ClFO_5$=479.0

CAS — 54063-32-0 (clobetasone); 25122-57-0 (clobetasone butyrate).

ATC — D07AB01; S01BA09.

ATC Vet — QD07AB01; QS01BA09.

UNII — 8U0H6X16EO.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Clobetasone Butyrate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in acetone and in dichloromethane. Protect from light.

Profile

Clobetasone butyrate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Clobetasone butyrate is also used for inflammatory eye disorders, as eye drops containing 0.1%. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies clobetasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Eumovate; *Austral.*: Becoderm-C†; Eumovate; *Austria*: Emovate; *Belg.*: Eumovate; *Braz.*: Eumovate; *Canad.*: Spectro Eczemacare; *Denm.*: Emovat; *Fin.*: Emovat; *Ger.*: Emovate; *Gr.*: Rettavate; *Hong Kong*: Eumovate; *Irl.*: Eumovate; *Israel*: Eumovate; *Ital.*: Clobet; Eumovate; Solderma; Visudoben; *Malaysia*: Eumovate; U-Closone; *Neth.*: Emovate; *NZ*: Becoderm-C†; Eumovate; *Port.*: Emovate; *S.Afr.*: Eumovate†; *Singapore*: Amisol; Eumovate; *Spain*: Emovate; *Swed.*: Emovat; *Switz.*: Emovate; *Thai.*: U-Closone; *Turk.*: Eumovate; *UK*: Eumovate; *Venez.*: Eumovate.

Multi-ingredient Preparations. *India*: Clobequad; Eumosone-G; Eumosone-M; Lozee-GM; Lozee-M; Lozee; *Israel*: Cicloderm-G; *Ital.*: Visudoben Antibiotico; Visudoben Decongestionante; *UK*: Trimovate.

Pharmacopoeial Preparations
BP 2014: Clobetasone Cream; Clobetasone Ointment.

Clocortolone Pivalate *(USAN, rINNM)* ⊗

CL-68; Clocortolona, pivalato de; Clocortolone, Pivalate de; Clocortoloni Pivalas; Pivalato de clocortolona; SH-863; Клокортолона Пивалат.

9α-Chloro-6α-fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-pivalate.

$C_{27}H_{36}ClFO_5$=495.0

CAS — 4828-27-7 (clocortolone); 34097-16-0 (clocortolone pivalate).

ATC — D07AB21.

ATC Vet — QD07AB21.

UNII — Q8L8IZH14X.

Pharmacopoeias. In *US*.

USP 36: (Clocortolone Pivalate). A white to yellowish-white, odourless powder. Sparingly soluble in alcohol; soluble in acetone; freely soluble in chloroform and in dioxan; slightly soluble in ether and in benzene. Store in airtight containers. Protect from light.

Profile

Clocortolone pivalate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1), as a 0.1% cream or ointment, in the treatment of various skin disorders. Clocortolone caproate has been used with the pivalate.

When applied topically, particularly to large areas, where the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Kaban†; Kabanimat†; *USA*: Cloderm.

Pharmacopoeial Preparations
USP 36: Clocortolone Pivalate Cream.

Cloprednol *(BAN, USAN, rINN)* ⊗

Cloprednolum; RS-4691; Клопреднол.

6-Chloro-11β,17α,21-trihydroxypregna-1,4,6-triene-3,20-dione.

$C_{21}H_{25}ClO_5$=392.9

CAS — 5251-34-3.

ATC — H02AB14.

ATC Vet — QH02AB14.

UNII — SYP56O3GJG.

Profile

Cloprednol is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); the anti-inflammatory activity of 2.5 mg of cloprednol is equivalent to about 5 mg of prednisolone. Cloprednol is given orally in various disorders for which corticosteroid therapy is helpful (p. 1597.3), in usual doses ranging from 1.25 to 12.5 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Syntestan.

Corticorelin *(rINN)* ⊗

Corticoliberin; Corticorelina; Corticoréline; Corticorelinum; Corticotrophin-releasing Hormone HLC; Corticotropin-releasing Factor; CRF; CRH; Hormona liberadora de corticotropina; Кортикорелин.

$C_{208}H_{344}N_{60}O_{63}S_2$=4757.5 (human); $C_{205}H_{339}N_{59}O_{63}S$=4670.3 (ovine)

CAS — 86784-80-7 (corticorelin (human)); 79804-71-0 (corticorelin (ovine)).

ATC — V04CD04.

ATC Vet — QV04CD04.

UNII — Y124TZ0513 (corticorelin ovine); 305OE8862Y (corticorelin human).

Corticorelin Triflutate *(rINNM)* ⊗

Corticorelin Trifluoroacetate; Corticorelina, triflutato de; Corticoréline, Triflutate de; Corticorelini Triflutas; Triflutato de corticorelina; Кортикорелина Трифлутат.

$C_{205}H_{339}N_{59}O_{63}S_xC_2HF_3O_2$(ovine)

CAS — 121249-14-7 (corticorelin ovine triflutate).

ATC — V04CD04.

ATC Vet — QV04CD04.

UNII — 56X547B17Q (corticorelin ovine triflutate).

NOTE. Corticorelin Ovine Triflutate is *USAN*.

Uses and Administration

Corticorelin is a polypeptide hypothalamic releasing hormone that stimulates the release of corticotropin (below) from the anterior pituitary. It is used in the differential diagnosis of Cushing's syndrome (see Diagnosis and Testing, below) and other adrenal disorders. Corticorelin is usually given as the triflutate, but doses are expressed in terms of corticorelin (human or ovine). A single dose of 100 micrograms, or of 1 microgram/kg, is given by intravenous injection over 30 seconds. Higher and more rapid doses have been used but may be associated with an increased risk of adverse effects (see below).

Corticorelin acetate is under investigation for the treatment of cerebral oedema associated with brain tumours.

Administration. Corticorelin was well absorbed after subcutaneous injection and bioavailability was calculated to be about 60 to 70%; absorption was slower with high doses, suggesting that it may be a saturable process. Given the retention of bioactivity, the subcutaneous route was considered an attractive alternative to intravenous use.[1]

1. Angst MS, *et al.* Pharmacokinetics, cortisol release, and hemodynamics after intravenous and subcutaneous injection of human corticotropin-releasing factor in humans. *Clin Pharmacol Ther* 1998; 64: 499–510.

Diagnosis and testing. Corticorelin may be used in the diagnosis of adrenal disorders including Cushing's syndrome (p. 2559.1). In the initial diagnosis of Cushing's syndrome, a dexamethasone-corticorelin test may be used to identify pseudo-Cushing's conditions such as depression or alcoholism in patients with mild hypercortisolism and equivocal results on other diagnostic tests. This combination is reportedly more accurate than either alone,[1] but it is cumbersome and difficult to carry out on an ambulatory basis.[2]

When a diagnosis of ACTH-dependent Cushing's syndrome has been established, corticorelin may be used for differential diagnosis of the subtype. Patients with pituitary Cushing's syndrome have an exaggerated increase in plasma-corticotropin and plasma-cortisol concentrations in response to corticorelin, whereas those with adrenal or ectopic syndrome generally have no response.[3,4] The corticorelin stimulation test is of comparable diagnostic efficacy to the dexamethasone suppression test,[5,6] although false results have been obtained with both tests.[2,5,7] Again, a combination of the dexamethasone and corticorelin tests is reportedly more accurate than either alone.[6] The most reliable test to distinguish between pituitary and nonpituitary forms of Cushing's syndrome is to measure the difference between central and peripheral concentrations of ACTH after giving corticorelin.[2] However, this requires sampling of central (petrosal) venous blood, an invasive procedure needing considerable expertise.

1. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; 269: 2232–8.
2. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; 138: 980–91.
3. Chrousos GP, *et al.* The corticotropin-releasing factor stimulation test: an aid in the evaluation of patients with Cushing's syndrome. *N Engl J Med* 1984; 310: 622–6.
4. Newell-Price J, *et al.* Optimal response criteria for the human CRH test in the differential diagnosis of ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab* 2002; 87: 1640–5.
5. Hermus AR, *et al.* The corticotropin-releasing-hormone test versus the high-dose dexamethasone test in the differential diagnosis of Cushing's syndrome. *Lancet* 1986; ii: 540–4.
6. Nieman LK, *et al.* The ovine corticotropin-releasing hormone stimulation test and the dexamethasone suppression test in the differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; 105: 862–7.
7. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; 88: 5593–5602.

Adverse Effects

Flushing of the face, neck, and upper chest, and mild dyspnoea may follow intravenous injection of corticorelin, and last for about 3 to 5 minutes. Prolonged flushing, tachycardia, hypotension, and chest tightness have been reported after large doses.

Effects on the cardiovascular system. Loss of consciousness, lasting for 10 seconds to 5 minutes, occurred in 4 patients, 2 of whom had Cushing's disease and one who had secondary adrenal insufficiency, after intravenous injection of corticorelin 200 micrograms.[1] The 2 patients with Cushing's disease had a slight accompanying fall in blood pressure. In a fourth patient, receiving corticosteroid and thyroid hormone replacement therapy, injection of corticorelin was associated with a sharp fall in systolic blood pressure and subsequent asystole. These serious adverse effects were not noted by others[2,3] and were variously attributed to impurities,[2] high dosage,[2] vasovagal syncope,[3] or to the fact that the corticorelin used in the study was of ovine rather than human origin.[3] The authors of the original study[1] have since stated[4] that lowering of the dose from 200 micrograms given intravenously over 10 seconds to 100 micrograms over 60 seconds has stopped serious adverse effects but that ovine corticorelin was still preferred because of its longer duration of action and lower incidence of hypotensive adverse effects. There has, however, been a further report of chest pain accompanied by a fall in blood pressure in a patient receiving corticorelin at a dose of 100 micrograms.[5]

1. Hermus A, *et al.* Serious reactions to corticotropin-releasing factor. *Lancet* 1983; i: 776.
2. Schulte HM, *et al.* Safety of corticotropin-releasing factor. *Lancet* 1983; i: 1222.
3. Oppermann D. Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; ii: 1031–2.
4. Hermus ARMM, *et al.* Safety of human and ovine corticotropin-releasing hormone. *Lancet* 1986; ii: 1032–3.
5. Paloma VC, *et al.* Chest pain after intravenous corticotropin-releasing hormone. *Lancet* 1989; i: 222.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: CRH; *Fr.*: Stimu-ACTH; *Ger.*: Cortirelı†; CRH; *Neth.*: CRH; *USA*: Acthrel.

Corticotropin *(BAN, rINN)* ⊗

ACTH; Adrenocorticotrofina; Adrenocorticotrophic Hormone; Adrenocorticotrophin; Corticotrofina; Corticotrophin Corticotropina; Corticotropine; Corticotropinum; Hormona adrenocorticotropa; Kortikotropiini; Kortikotropin; Кортикотропин.

CAS — 9002-60-2 (corticotropin); 9050-75-3 (corticotropin zinc hydroxide); 8049-55-6 (corticotropin zinc hydroxide).

ATC — H01AA01.

ATC Vet — QH01AA01.

UNII — K0U68Q2TXA (corticotropin); 0480S42OTR (corticotropin bovine/ovine); FP33F50XKB (corticotropin porcine).

Pharmacopoeias. In *US* as preparations for injection.

Units

5 units of porcine corticotropin for bioassay are contained in about 50 micrograms (with lactose 5 mg) in one ampoule of the third International Standard (1962).

Uses and Administration

Corticotropin is a naturally occurring hormone of the anterior lobe of the pituitary gland. It stimulates the adrenal glands to secrete adrenocortical hormones, especially cortisol (hydrocortisone), some mineralocorticoids such as corticosterone, and, to a lesser extent, androgens. It has little effect on aldosterone secretion, which proceeds independently.

Secretion of corticotropin by the functioning pituitary gland is controlled by the release of corticorelin from the hypothalamus and is also regulated by a negative feedback mechanism involving concentrations of circulating glucocorticoids. Conditions of stress may also stimulate secretion.

Corticotropin may be used diagnostically to investigate adrenocortical insufficiency. It has also been used therapeutically in most of the conditions (with the exception of the adrenal deficiency states and adrenocortical overactivity) for which systemic corticosteroid therapy is indicated (p. 1597.3). Such use is now fairly limited. However, corticotropin may be used in certain neurological disorders such as infantile spasms and multiple sclerosis. The synthetic polypeptide tetracosactide (p. 1648.1), which has the same amino-acid sequence as the first 24 residues of human corticotropin, may be used as an alternative

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QD07XB05; QD10AA03; QH02AB02; QR01AD03; QS01BA01; QS01CB01; QS02BA06; QS03BA01.
UNII — 7S5I7G3JQL.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Dexamethasone). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Dexamethasone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol, in acetone, in dioxan, and in methyl alcohol; slightly soluble in chloroform; very slightly soluble in ether.

Dexamethasone Acetate

(BANM, USAN, rINNM) ⊗

Acetato de dexametasona; Deksametasoniasetaatti; Deksametazono acetatas; Dexametasona, acetato de; Dexametasonacetat; Dexametazon-acetát; Dexamethasonacetat; Dexamethason-acetát; Dexaméthasone, acétate de; Dexamethasoni Acetas; Дексаметазона Ацетат.

Dexamethasone 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 1177-87-3 (anhydrous dexamethasone acetate); 55812-90-3 (dexamethasone acetate monohydrate).

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

UNII — E2287TKU04 (dexamethasone acetate); K7V8P532WP (anhydrous dexamethasone acetate); DWN2WN457X (dexamethasone acetate monohydrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), and *Viet.*

Int. and *US* allow the anhydrous form or the monohydrate.

Ph. Eur. 8: (Dexamethasone Acetate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Protect from light.

USP 36: (Dexamethasone Acetate). It contains one molecule of water of hydration or is anhydrous. A clear, white to off-white, odourless powder. Practically insoluble in water; freely soluble in acetone, in dioxan, and in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Dexamethasone Isonicotinate

(BANM, rINNM) ⊗

Deksametasoniisonikotinaatti; Deksametazonu izonikotynian; Dexametasona, isonicotinato de; Dexametasonisonikotinat; Dexaméthasone, Isonicotinate de; Dexamethasoni Isonicotinas; Dexamethasonisonicotinat; Dexamethasonisonikotinát; Isonicotinato de dexametasona; Дексаметазона Изоникотинат.

Dexamethasone 21-isonicotinate.

$C_{28}H_{32}FNO_6$=497.6

CAS — 2265-64-7.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

UNII — 8LGC0BOA71.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dexamethasone Isonicotinate). A white or almost white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone.

Dexamethasone Phosphate *(BANM, rINNM)* ⊗

Dexametasona, fosfato de; Dexaméthasone, Phosphate de; Dexamethasoni Phosphas; Fosfato de dexametasona; Дексаметазона Фосфат.

Dexamethasone 21-(dihydrogen phosphate).

$C_{22}H_{30}FO_8P$=472.4

CAS — 312-93-6.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

UNII — 2BP70L44PR.

Dexamethasone Sodium Metasulfobenzoate *(rINNM)* ⊗

Dexametasona, metasulfobenzoato sódico de; Dexaméthasone Métasulfobenzoate Sodique; Dexamethasone Sodium Metasulphobenzoate (BANM); Dexamethasone Sodium Metasulphobenzoate; Metasulfobenzoato sódico de dexametasona; Natrii Dexamethasoni Metasulfobenzoas; Натрий Метасульфобензоат Дексаметазон.

Dexamethasone 21-(sodium *m*-sulphobenzoate).

$C_{29}H_{28}FNaO_8S$=598.6

CAS — 3936-02-5.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

UNII — 4T1RAI19H8.

Dexamethasone Sodium Phosphate

(BANM, rINNM) ⊗

Deksametasoninatriumfosfaatti; Deksametazon Sodyum Fosfat; Deksametazono natrio fosfatas; Dexametasona, fosfato sódico de; Dexametasonnatriumfosfat; Dexametazon-nátrium-foszfát; Dexamethasondihydrogenphosphat-Dinatrium; Dexaméthasone, phosphate sodique de; Dexamethasone Phosphate Sodium; Dexamethason-fosfát sodná sůl; Dexamethasoni Natrii Phosphas; Fosfato sódico de dexametasona; Natrii Dexamethasoni Phosphas; Sodium Dexamethasone Phosphate; Натрия Дексаметазона Фосфат.

Dexamethasone 21-(disodium orthophosphate).

$C_{22}H_{28}FNa_2O_8P$=516.4

CAS — 2392-39-4.

ATC — A01AC02; C05AA09; D07AB19; H02AB02; R01AD03; S01BA01; S02BA06; S03BA01.

ATC Vet — QA01AC02; QC05AA09; QD07AB19; QH02AB02; QR01AD03; QS01BA01; QS02BA06; QS03BA01.

UNII — AI9376Y64P.

NOTE. DSP is a code approved by the BP 2014 for use on single unit doses of eye drops containing dexamethasone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., US,* and *Viet.*

Ph. Eur. 8: (Dexamethasone Sodium Phosphate). A white or almost white, very hygroscopic, powder. It exhibits polymorphism. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 7.5 to 9.5. Store in airtight containers. Protect from light.

USP 36: (Dexamethasone Sodium Phosphate). A white or slightly yellow, crystalline powder. Is odourless or has a slight odour of alcohol, and is exceedingly hygroscopic. Soluble 1 in 2 of water; slightly soluble in alcohol; insoluble in chloroform and in ether; very slightly soluble in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Uses and Administration

Dexamethasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 750 micrograms of dexamethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It has been used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (p. 1597.3), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred. Its lack of mineralocorticoid properties makes dexamethasone particularly suitable for treating conditions where water retention would be a disadvantage.

The dose may be expressed in terms of the base, and the following are each equivalent to about 1 mg of dexamethasone:

- dexamethasone acetate 1.1 mg
- dexamethasone isonicotinate 1.3 mg
- dexamethasone phosphate 1.2 mg
- dexamethasone sodium metasulfobenzoate 1.5 mg
- dexamethasone sodium phosphate 1.3 mg

However, esterification generally alters potency and compounds with equivalent dexamethasone content may not have equivalent clinical effect.

Dexamethasone sodium phosphate 1.1 mg is equivalent to about 1 mg of dexamethasone phosphate.

For **oral administration** dexamethasone is given in usual doses of 0.5 to 10 mg daily. Dexamethasone is also used orally in the dexamethasone suppression tests for the diagnosis of Cushing's syndrome (for further details see under Diagnosis and Testing, p. 1632.1).

For **parenteral administration** in *intensive therapy* or in *emergencies,* the sodium phosphate ester may be given intravenously by injection or infusion or intramuscularly by injection; doses are sometimes expressed in terms of the free alcohol, the phosphate, or the sodium phosphate and confusion has sometimes arisen in the literature because of these variations. Initial doses used, expressed in terms of dexamethasone phosphate, range from about 0.5 to 24 mg daily (about 0.4 to 20 mg of dexamethasone). Intravenous doses equivalent to 2 to 6 mg/kg of dexamethasone phosphate given slowly over a minimum period of several minutes have been suggested for the treatment of severe shock. These high doses may be repeated within 2 to 6 hours and this treatment should be continued only until the patient's condition is stable and usually for no longer than 48 to 72 hours. Alternatively, the initial intravenous injection may be followed by a continuous intravenous infusion of 3 mg/kg per 24 hours.

Dexamethasone sodium phosphate is also used in the treatment of *cerebral oedema* caused by malignancy. An initial intravenous dose equivalent to 10 mg of dexamethasone phosphate is followed by 4 mg intramuscularly every 6 hours until the symptoms of oedema subside. A response is usually obtained after 12 to 24 hours and dosage may be reduced after 2 to 4 days, then gradually stopped over 5 to 7 days. A much higher dosage schedule has also been suggested for use in acute life-threatening cerebral oedema. An initial intravenous dose equivalent to 50 mg of dexamethasone phosphate is followed by 8 mg intravenously every 2 hours for the first 3 days of treatment. The dose is then reduced to 4 mg every 2 hours on day 4, followed by 4 mg every 4 hours on days 5 to 8 of treatment. Thereafter, the dose is gradually reduced by 4 mg daily. A maintenance dose of 2 mg given by intravenous or intramuscular injection 2 or 3 times daily has been used in patients with recurrent or inoperable neoplasms.

Dexamethasone is given intravenously and orally for the prevention of *nausea and vomiting* induced by cancer chemotherapy (see p. 1632.3).

The sodium phosphate ester is given by **intra-articular, intralesional,** or **soft-tissue injection.** For intra-articular injection doses equivalent to 0.8 to 4 mg of dexamethasone phosphate are used depending upon the size of the joint. For soft-tissue injection doses of 2 to 6 mg are used. Injections are repeated every 3 to 5 days to every 2 to 3 weeks. Dexamethasone acetate has also been given by intramuscular, intra-articular, soft-tissue, and intralesional injection.

For **topical** application in the treatment of various *skin disorders,* either dexamethasone or its esters may be used. Concentrations may be expressed in terms of dexamethasone, commonly in the range of 0.02 to 0.1% in preparations such as creams, ointments, and lotions. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Dexamethasone is also used topically in various *eye and ear disorders,* and preparations may contain either dexamethasone or one of its esters. Concentrations are often expressed in terms of dexamethasone or dexamethasone phosphate and are commonly 0.05 to 0.1% for eye or ear drops and eye ointments.

For allergic rhinitis (p. 612.1) and other allergic or inflammatory *nasal conditions,* a nasal spray containing dexamethasone isonicotinate is available; the acetate, phosphate, sodium phosphate, and sodium metasulfobenzoate have also been used.

A biodegradable **intravitreal implant** containing dexamethasone is used for the treatment of macular oedema after branch or central retinal vein occlusion.

Other esters of dexamethasone that have occasionally been used include the hemisuccinate, linoleate, palmitate, pivalate, propionate, sodium succinate, tebutate, and valerate.

The phenpropionate and troxundate esters have been used in veterinary medicine.

Dexamethasone-releasing stents may be used to reduce restenosis after coronary artery stent placement.

Alcohol withdrawal syndrome. Dexamethasone was reported to be effective in a patient with benzodiazepine-resistant delirium tremens[1] and resolved symptoms of alcohol withdrawal syndrome resistant to other treatments in another 110 patients.[2] However, a subsequent small study found no evidence that dexamethasone was effective.[3]

1. Fischer DK, *et al.* Efficacy of dexamethasone in benzodiazepine-resistant delirium tremens. *Lancet* 1988; **i**: 1340–1.
2. Pol S, *et al.* Dexamethasone for alcohol withdrawal. *Ann Intern Med* 1991; **114**: 705–6.
3. Adinoff B, Pols B. Dexamethasone in the treatment of the alcohol withdrawal syndrome. *Am J Drug Alcohol Abuse* 1997; **23**: 615–22.

Amyloidosis. For mention of the use of dexamethasone in patients with amyloidosis, see p. 819.3.

Blood disorders. High-dose pulsed dexamethasone therapy has been found useful in some patients with immune thrombocytopenia (p. 1606.1).

Cerebral oedema. Corticosteroids, usually dexamethasone, play an important role in the treatment of cerebral oedema in malignancy (see Raised Intracranial Pressure, p. 1271.3), and dexamethasone is advocated for

the cerebral oedema associated with high-altitude disorders (see below).

Congenital adrenal hyperplasia. Because of its lack of mineralocorticoid properties, dexamethasone has little advantage in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2), in which mineralocorticoid therapy must be given, and its potency means that dose titration to avoid toxicity can be difficult in infants and children, even with the non-salt-losing form. However, it may be useful in adults with forms of the syndrome that do not require mineralocorticoid replacement. It has also been given antenatally to the mother to prevent virilisation of female fetuses.

Diagnosis and testing. *CUSHING'S SYNDROME.* Dexamethasone has been used to differentiate Cushing's disease (adrenal hyperplasia caused by defects of pituitary origin) from other forms of Cushing's syndrome (caused by ectopic ACTH secretion from non-pituitary tumours or by cortisol secretion from adrenal tumours). The dexamethasone suppression test as first proposed[1] involved giving oral dexamethasone in low doses of 500 micrograms four times daily for 8 doses followed by higher doses of 2 mg four times daily for 8 doses. In the low-dose tests the urinary excretion of cortisol and 17-hydroxycorticosteroids is suppressed in healthy persons but not in patients and in the high-dose tests the excretion is still not suppressed in those with Cushing's syndrome but is partially suppressed in those with Cushing's disease. Because this test usually involves patients being admitted to hospital for urine collection over several days and because false-negative responses are reported to be fairly frequent, more rapid and reliable tests have been sought. The low-dose test plus measurement of serum-cortisol concentrations and the excretion of free cortisol in urine over 24 hours has been suggested[2] to be a reliable method for screening for Cushing's syndrome. In the UK a single dose of 1 mg of dexamethasone given at night is often used and is considered sufficient to inhibit corticotropin secretion for 24 hours in most subjects. In another variation[3] a single dose of dexamethasone 8 mg has been given at night and plasma-cortisol concentrations measured the next day; this test (known as the overnight high-dose dexamethasone suppression test) has again been said to be a practical and reliable alternative for the differential diagnosis of Cushing's syndrome.

Further variations in the dexamethasone suppression test have included giving a continuous intravenous infusion of dexamethasone at a rate of 1 mg/hour for 7 hours, with hourly measurement of blood-cortisol concentrations.[4] Initial results indicate that this variation produces a lower number of false-positive diagnoses than the test using oral dexamethasone. Other alternatives are a combined low-dose dexamethasone suppression test and corticotropin-releasing hormone (corticorelin) test,[5] or combination of a dexamethasone suppression test with a metyrapone test.[6]

Reviews[7,8] of diagnostic tests for Cushing's syndrome have outlined both the advantages and disadvantages of tests using dexamethasone. These suggested that where there is suspicion of Cushing's syndrome, the overnight low-dose dexamethasone suppression test may be used as part of a range of measures, and that the dexamethasone-corticorelin test may be useful when there are equivocal results from initial screening. In a study to assess the efficacy of low-dose dexamethasone, some patients were found to suppress plasma or urinary steroid concentrations to levels previously thought to exclude a diagnosis of Cushing's syndrome. The authors concluded that these low-dose tests should not be used as the sole criterion for diagnosis, and that a much lower value for serum cortisol should be used to achieve adequate sensitivity.[9] In the differentiation of ACTH-dependent and ACTH-independent forms of Cushing's syndrome, one review[7] suggested that the high-dose dexamethasone suppression test cannot be recommended because of poor specificity.

For further discussion of the various methods used for the diagnosis of Cushing's syndrome and details of its management, see p. 2559.1. Various drugs may interfere with the dexamethasone suppression test.

1. Liddle GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 1960; **20**: 1539–60.
2. Kennedy L, *et al.* Serum cortisol concentrations during low dose dexamethasone suppression test to screen for Cushing's syndrome. *BMJ* 1984; **289**: 1188–91.
3. Tyrrell JB, *et al.* An overnight high-dose dexamethasone suppression test for rapid differential diagnosis of Cushing's syndrome. *Ann Intern Med* 1986; **104**: 180–6.
4. Blemond P, *et al.* Continuous dexamethasone infusion for seven hours in patients with the Cushing syndrome: a superior differential diagnostic test. *Ann Intern Med* 1990; **112**: 738–42.
5. Yanovski JA, *et al.* Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration: a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA* 1993; **269**: 2232–8.
6. Avgerinos PC, *et al.* The metyrapone and dexamethasone suppression tests for the differential diagnosis of the adrenocorticotropin-dependent Cushing syndrome: a comparison. *Ann Intern Med* 1994; **121**: 318–27.
7. Raff H, Findling JW. A physiologic approach to diagnosis of the Cushing syndrome. *Ann Intern Med* 2003; **138**: 980–91.
8. Arnaldi G, *et al.* Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; **88**: 5593–5602.
9. Findling JW, *et al.* The low-dose dexamethasone suppression test: a reevaluation in patients with Cushing's syndrome. *J Clin Endocrinol Metab* 2004; **89**: 1222–6.

DEPRESSION. The Health and Public Policy Committee of the American College of Physicians noted that the dexamethasone suppression test for depression (p. 398.1) was based on the premise that endogenously depressed patients have shown pituitary-adrenal axis abnormalities but had been found to have a low sensitivity for detecting depression. It was of unproven value and was not recommended as a screening test.[1] Nonetheless, interest remains; studies[2–6] have shown conflicting results.

1. Young M, Schwartz JS. The dexamethasone suppression test for the detection, diagnosis, and management of depression. *Ann Intern Med* 1984; **100**: 307–8.
2. Coryell W. DST abnormality as a predictor of course in major depression. *J Affect Disord* 1990; **19**: 163–9.
3. Plocka-Lewandowska M, *et al.* Dexamethasone suppression test and suicide attempts in schizophrenic patients. *Eur Psychiatry* 2001; **16**: 428–31.
4. Coryell W, Schlesser M. The dexamethasone suppression test and suicide prediction. *Am J Psychiatry* 2001; **158**: 748–53.
5. Black DW, *et al.* The relationship between DST results and suicidal behavior. *Ann Clin Psychiatry* 2002; **14**: 83–8.
6. Yerevanian BI, *et al.* The dexamethasone suppression test as a predictor of suicidal behavior in unipolar depression. *J Affect Disord* 2004; **83**: 103–8.

High-altitude disorders. Dexamethasone is effective in the prevention of symptoms of acute mountain sickness (p. 1276.2), for which mild cerebral oedema may be a contributing factor, but it is not generally considered suitable for routine prophylaxis because of concern about its adverse effects. In the treatment of acute severe mountain sickness, which may involve the development of pulmonary and cerebral oedema, the mandatory treatment is immediate descent, and drug therapy is mainly adjunctive, to facilitate descent or maintain the patient until descent is possible. Under these circumstances dexamethasone and oxygen form the mainstays of treatment.

References.

1. Ferrazzini G, *et al.* Successful treatment of acute mountain sickness with dexamethasone. *BMJ* 1987; **294**: 1380–2.
2. Ellsworth AJ, *et al.* A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. *Am J Med* 1987; **83**: 1024–30.
3. Montgomery AB, *et al.* Effects of dexamethasone on the incidence of acute mountain sickness at two intermediate altitudes. *JAMA* 1989; **261**: 734–6.
4. Levine BD, *et al.* Dexamethasone in the treatment of acute mountain sickness. *N Engl J Med* 1989; **321**: 1707–13.
5. Keller H-R, *et al.* Simulated descent v dexamethasone in treatment of acute mountain sickness: a randomised trial. *BMJ* 1995; **310**: 1232–5.
6. Dumont L, *et al.* Efficacy and harm of pharmacological prevention of acute mountain sickness: quantitative systematic review. *BMJ* 2000; **321**: 267–72.

Hirsutism. Unbound testosterone concentrations were consistently elevated in 32 hirsute women; when concentrations were suppressed to normal by dexamethasone 0.5 to 1 mg at night hirsutism was generally improved or ceased to progress after 8 to 10 months of treatment.[1] Other studies have shown only a modest improvement[2] or no improvement at all[3] in hirsutism when treated with dexamethasone. Addition of dexamethasone to anti-androgen therapy appeared to prolong the duration of remission in a later study.[4]

The mainstay of drug treatment for hirsutism tends to be an anti-androgen such as cyproterone or spironolactone (p. 2262.1). Although low dose corticosteroids can suppress adrenal androgen production, careful consideration of the risks and benefits is advisable, especially since therapy for hirsutism may have to be given long-term.

1. Paulson JD, *et al.* Free testosterone concentration in serum: elevation is the hallmark of hirsutism. *Am J Obstet Gynecol* 1977; **128**: 851–7.
2. Carmina E, Lobo RA. Peripheral androgen blockade versus glandular androgen suppression in the treatment of hirsutism. *Obstet Gynecol* 1991; **78**: 845.
3. Rittmaster RS, Thompson DL. Effect of leuprolide and dexamethasone on hair growth and hormone levels in hirsute women: the relative importance of the ovary and the adrenal in the pathogenesis of hirsutism. *J Clin Endocrinol Metab* 1990; **70**: 1096–1102.
4. Carmina E, Lobo RA. The addition of dexamethasone to antiandrogen therapy for hirsutism prolongs the duration of remission. *Fertil Steril* 1998; **69**: 1075–9.

Malaria. Corticosteroids, especially dexamethasone, have been used in cerebral malaria (p. 644.1) in the belief that their anti-inflammatory effect would reduce cerebral oedema. However, studies have shown that cerebral oedema does not play a significant role in the pathophysiology of cerebral malaria and, indeed, double-blind studies using both moderate doses (2 mg/kg) and high doses (11 mg/kg) of dexamethasone intravenously over 48 hours found no reduction in death rates. Thus it is now considered that corticosteroids have no place in the treatment of cerebral malaria.[1]

1. Prasad K, Garner P. Steroids for treating cerebral malaria. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 1999 (accessed 12/05/05).

Malignant neoplasms. Dexamethasone has been used in some regimens for the treatment of malignancy, for example in acute lymphoblastic leukaemia (p. 692.3) and multiple myeloma (p. 699.2).

Meningitis. The role of corticosteroids in the adjuvant treatment of bacterial meningitis (p. 191.1) has been the subject of considerable debate. Studies have shown conflicting results.[1–3] However, a systematic review[4] concluded that there was evidence of benefit, particularly in reducing deafness and short-term neurological sequelae in children and adults in high-income countries; mortality and long-term neurological sequelae were not reduced. No beneficial effect was seen in low-income countries. It has been suggested[4] that a 4-day regimen of dexamethasone (0.6 mg/kg daily) be given to adults and children in high-income countries, preferably before or with the first dose of antibacterial. Implementation of a nationwide policy to give routine adjunctive intravenous dexamethasone (10 mg every 6 hours for 4 days) with or before the first dose of parenteral antibacterial for the treatment of adults with pneumococcal meningitis in a European country resulted in a 10% decrease in mortality (from 30 to 20%); adjunctive dexamethasone treatment appeared to be more effective in those 55 years of age and older.[5]

1. Molyneux EM, *et al.* Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002; **360**: 211–18.
2. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; **347**: 1549–56.
3. Thwaites GE, *et al.* Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med* 2004; **351**: 1741–51.
4. Brouwer MC, *et al.* Corticosteroids for acute bacterial meningitis. Available in The Cochrane Database of Systematic Reviews; Issue 5. Chichester: John Wiley; 2010 (accessed 08/03/12).
5. Brouwer MC, *et al.* Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology* 2012; **79**: 1533–9.

Nausea and vomiting. Dexamethasone has antiemetic properties, particularly against acute and delayed vomiting induced by cancer chemotherapy[1] (p. 1811.3). It may be used alone for prevention of acute symptoms associated with moderately-emetogenic treatment and is combined with a 5-HT_3 antagonist for highly-emetogenic treatment. Typical dosage regimens have been dexamethasone 4 to 8 mg orally immediately before moderately-emetogenic chemotherapy and 20 mg by intravenous injection for more severely emetogenic chemotherapy. Dexamethasone is the drug of choice for prevention of delayed symptoms, given alone or with other antiemetics. A typical oral dose is 8 mg twice daily for 2 to 4 days. Dexamethasone is also effective for the prevention of postoperative nausea and vomiting,[2] and may be used to manage nausea and vomiting in palliative care.

1. Ioannidis JPA, *et al.* Contribution of dexamethasone to control of chemotherapy-induced nausea and vomiting: a meta-analysis of randomized evidence. *J Clin Oncol* 2000; **18**: 3409–22.
2. Henzi I, *et al.* Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg* 2000; **90**: 186–94.

Opportunistic mycobacterial infections. Dexamethasone in doses of 1 to 4 mg daily was associated with weight gain, reduction in fever, and an improved sense of well-being in 5 patients with HIV and disseminated *Mycobacterium avium* complex infection.[1] Combination antimycobacterial therapy for nontuberculous mycobacterial infections (p. 194.1) was also given. Similar results have been noted by others.[2]

1. Wormser GP, *et al.* Low-dose dexamethasone as adjunctive therapy for disseminated Mycobacterium avium complex infections in AIDS patients. *Antimicrob Agents Chemother* 1994; **38**: 2215–17.
2. Dorman SE, *et al.* Adjunctive corticosteroid therapy for patients who treatment for disseminated Mycobacterium avium complex infection has failed. *Clin Infect Dis* 1998; **26**: 682–6.

Respiratory disorders. Corticosteroids such as dexamethasone have been given antenatally to mothers at risk of premature delivery in order to hasten fetal lung maturation and help prevent *neonatal respiratory distress syndrome* (p. 1608.3) and *bronchopulmonary dysplasia* (p. 1602.1). Neonatal dexamethasone has been reported to improve pulmonary outcome and assist weaning from mechanical ventilation in infants that have developed bronchopulmonary dysplasia.

Dexamethasone is also one of the drugs of choice for the management of severe *croup* (see p. 1603.3). However, as with other corticosteroids (p. 1601.3) it appears to be of little value in *bronchiolitis*.[1–3]

1. Rooseveli G, *et al.* Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996; **348**: 292–5.
2. Klassen TP, *et al.* Dexamethasone in salbutamol-treated inpatients with acute bronchiolitis: a randomized controlled trial. *J Pediatr* 1997; **130**: 191–6.
3. Corneli HM, *et al.* A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007; **357**: 331–9.

Retinopathy of prematurity. For a suggestion that antenatal dexamethasone might be helpful in the prophylaxis of retinopathy of prematurity, see p. 2120.3. For mention of

the uncertain effect of neonatal dexamethasone on retinopathy of prematurity, see Effects on the Neonate, under Adverse Effects below.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Dexamethasone has little or no effect on sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on the neonate. The adverse effects of corticosteroids on the fetus are discussed under Pregnancy on p. 1619.1.

Adverse effects noted in premature neonates with bronchopulmonary dysplasia (p. 1602.1) receiving dexamethasone treatment to enable weaning from assisted ventilation have included hypertension[1-4] often accompanied by bradycardia,[1,2] gastroduodenal perforation,[4-6] ulceration and thinning of the gastric wall,[5] development of a catabolic state,[4,7] renal calcification,[8,9] and transient myocardial hypertrophy.[10-13] There is some evidence of a suppressive effect on motor activity and spontaneous movement.[14] It has been postulated that neonatal dexamethasone may both increase[15] and decrease[16] retinopathy of prematurity; its true effect is uncertain.[17]

There is also a concern that longer term development of the child may be adversely affected.[18,19] Although data are scanty, a meta-analysis[20] has concluded that postnatal use of corticosteroids to treat or prevent bronchopulmonary dysplasia is associated with dramatic increases in the incidence of cerebral palsy and neurodevelopmental impairment, and suggested that such use should be abandoned.

Pulsed dosage may reduce the adverse effects but may also reduce efficacy.[21]

1. Ohlsson A, Heyman E. Dexamethasone-induced bradycardia. *Lancet* 1988; ii: 1074.
2. Puntis JWL, *et al.* Dexamethasone-induced bradycardia. *Lancet* 1988; ii: 1372.
3. Marinelli KA, *et al.* Effects of dexamethasone on blood pressure in premature infants with bronchopulmonary dysplasia. *J Pediatr* 1997; 130: 594–602.
4. Stark AR, *et al.* Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. *N Engl J Med* 2001; 344: 95–101.
5. Ng PC, *et al.* Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; 66: 1164–6.
6. Smith H, Sinha S. Gastrointestinal complications associated with dexamethasone treatment. *Arch Dis Child* 1992; 67: 667.
7. Macdonald PD, *et al.* A catabolic state in dexamethasone treatment of bronchopulmonary dysplasia. *Arch Dis Child* 1990; 65: 560–1.
8. Kamitsuka MD, Peloquin D. Renal calcification after dexamethasone in infants with bronchopulmonary dysplasia. *Lancet* 1991; 337: 626.
9. Narendra A, *et al.* Nephrocalcinosis in preterm babies. *Arch Dis Child Fetal Neonatal Ed* 2001; 85: F207–F213.
10. Werner JC, *et al.* Hypertrophic cardiomyopathy associated with dexamethasone therapy for bronchopulmonary dysplasia. *J Pediatr* 1992; 120: 286–91.
11. Bensky AS, *et al.* Cardiac effects of dexamethasone in very low birth weight infants. *Pediatrics* 1996; 97: 818–21.
12. Skelton R, *et al.* Cardiac effects of short course dexamethasone in preterm infants. *Arch Dis Child* 1998; 78: F133–F137.
13. Zecca E, *et al.* Cardiac adverse effects of early dexamethasone treatment in preterm infants: a randomized clinical trial. *J Clin Pharmacol* 2001; 41: 1075–81.
14. Bos AF, *et al.* Qualitative assessment of general movements in high-risk preterm infants with chronic lung disease requiring dexamethasone therapy. *J Pediatr* 1998; 132: 300–6.
15. Batton DG, *et al.* Severe retinopathy of prematurity and steroid exposure. *Pediatrics* 1992; 90: 534–6.
16. Sobel DB, Philip AGS. Prolonged dexamethasone therapy reduces the incidence of cryotherapy for retinopathy of prematurity in infants of less than 1 kilogram birth weight with bronchopulmonary dysplasia. *Pediatrics* 1992; 90: 529–33.
17. Ehrenkranz RA. Steroids, chronic lung disease, and retinopathy of prematurity. *Pediatrics* 1992; 90: 646–7.
18. Greenough A. Gains and losses from dexamethasone for neonatal chronic lung disease. *Lancet* 1998; 352: 835–6.
19. Shinwell ES, *et al.* Early postnatal dexamethasone treatment and increased incidence of cerebral palsy. *Arch Dis Child Fetal Neonatal Ed* 2000; 83: F177–F181.
20. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. *BMC Pediatr* 2001; 1: 1. Available at: http://www.biomedcentral.com/1471-2431/1/1 (accessed 27/04/04)
21. Bloomfield FH, *et al.* Side effects of 2 different dexamethasone courses for preterm infants at risk of chronic lung disease: a randomized trial. *J Pediatr* 1998; 133: 395–400.

Effects on the nervous system. Paraesthesia, usually localised to the perineum, has been associated with the intravenous use of dexamethasone sodium phosphate (see p. 1617.3).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dexamethasone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3. Various drugs may interfere with the dexamethasone suppression test.

Antiepileptics. As mentioned on p. 544.2, dexamethasone may decrease or increase plasma concentrations of *phenytoin*. Like other enzyme-inducing drugs, phenytoin also has the potential to increase the metabolism of dexamethasone. There have been reports of false positive dexamethasone suppression tests (see Diagnosis and Testing, p. 1632.1) in patients taking *carbamazepine*.[1]

1. Ma RCW, *et al.* Carbamazepine and false positive dexamethasone suppression tests for Cushing's syndrome. *BMJ* 2005; 330: 299–300.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Dexamethasone is readily absorbed from the gastrointestinal tract. Its biological half-life in plasma is about 190 minutes. Binding of dexamethasone to plasma proteins is about 77%, which is less than for most other corticosteroids. Up to 65% of a dose is excreted in urine within 24 hours. Clearance in premature neonates is reported to be proportional to gestational age, with a reduced elimination rate in the most premature. It readily crosses the placenta with minimal inactivation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Decadron; Degabina†; Dexalaf; Dexalergin; Dexameral; Dexatotal; Duo-Decadron; Fadametasona; Gotabiotic D; Ingedex†; Isopto Maxidex; Lormine; Nexadron; Rapi-Dexacort; Rupedex; Sedesterol; Trofinan; *Austral.*: Dexmethsone; Maxidex; *Austria*: Dexabene; Fortecortin; Monodex; *Belg.*: Acidexam; Dexa-Sine†; Maxidex; *Braz.*: Bexeton; Cetadex; Cortitop; Decadron; Decadronal; Deflaren; Dexacilin†; Dexaden; Dexadermil; Dexaglos; Dexagreen; Dexamesson; Dexametax; Dexaminor; Dexanil; Dexason; Dexazona; Lisoderme; Maxidex; Metadex; Metaxon; Minidex; Neodex; Topidexa†; Uni Dexa; *Canad.*: Ak-Dex; Dexasone; Diodex; Maxidex; Ozurdex; *Chile*: Cortyk; Maxidex; Oradexon; *China*: 999 Piyanping (999 皮炎平); Di Da (迪达); Duo Ta Ke Mei (多他可美); Ge Da Li (戈达利); Limethason (利美达松); Surodex (思诺迪清); Xi Luo An (息洛安); Yi Ke Tie (意可贴); You Nuo Ping (优诺平); Zhong Yi Mei Song (众益美松); *Cz.*: Baycuten†; Dexaltin†; Dexamed; Fortecortin; Ozurdex; *Denm.*: Maxidex; Ozurdex; *Fin.*: Kaarmepakkaus†; Oftan Dexa; Oradexon; *Fr.*: Dectancyl; Dexafree; Maxidex; Neodex; Ozurdex; *Ger.*: afpred-DEXA†; Axidexa†; Cortidexason; Dexa Loscon mono; dexaclinit; Dexa-Effekton; Dexa-Ophtal; Dexa-ratiopharm; Dexa-Rhinospray Mono†; Dexa-Rhinospray N; Dexa-sine; Dexa; Dexabene; Dexabeta†; DexaEDO; Dexaflam†; Dexagalen; Dexagel; Dexahexal†; Dexapos; Fortecortin; InfectoDexaKrupp; Isopto Dex; Lipotalon; Monodex; Ozurdex; Solupen; Solutio Cordes Dexa N; Spersadex; Totocortin†; Tuttozem N; *Gr.*: Decadron; Dexa-Sine; Dexacollyre; Dexafar; Dexamed†; Dexaton; Dexatopic†; Maxidex; Oradexon; Soldesanil; Thilodexine; *Hong Kong*: CP-Dexa†; Dexaltin; Dexamed; Dexasone; Dexmetha†; Dexmethsone; Limethason†; Maxidex; *Hung.*: Dexa; Maxidex; Oradexon†; *India*: Decdak ST; Decdan; Decolite; Decrina; Dedron; Deksa; Demisone; Deosone; Dex-V; Dex; Dexacip; Dexaject; Dexalab; Dexamac; Dexamag; Dexamine; Dexane; Dexar; Dexariv; Dexasia; Dexasone; Dexona; Idizone; Intradex; Losone; Low-Dex; Mexa; Millicortenol; Wymesone; *Indon.*: Camidexon; Cetadexon†; Corsona; Cortidex; Danasone†; Decilone†; Dellamethasone†; Dexa-M; Etason; Fortecortin†; Indexon; Inthesa-5†; Kalmethasone; Lanadexon; Licodexon; Molacort; Nufadex; Oradexon; Prodexon; Pycameth; Pyradexon†; Scandexon; *Irl.*: Dexsol; Maxidex; Ozurdex; *Israel*: Dexacort; Maxidex; Ozurdex; Sterodex; *Ital.*: Capital; Decadron; Dermadex; Dexamono; Etacortilen; Luxazone; Megacort; Soldesam; Visumetazone; *Jpn*: Limethason; Methaderm; Voalla; *Malaysia*: Decan; Dexalone; Dexaltin; Dexasone; Maxidex; Penatone; Roximeth; *Mex.*: Adrecort; Alin; Azona; Beminex; Bexine†; Cortidex; Cryometasona; Decadron; Decadronal; Decorex; Dexafrin; Dexagrin; Dexal; Dexamilan; Dexicart†; Dexilal; Dexona†; Dibasona; Etacortilen; Examsa†; Indarzona-N†; Lergosin; Maxidex; Metax; Pardex; Reusan; Taprodex†; Taxyl; Wiserdex; *Neth.*: Dexa-POS; Dexsol; Oradexon; Ozurdex; *Norw.*: Isopto Maxidex; Ozurdex; Spersadex; *NZ*: Maxidex; *Philipp.*: Adrecort; Cordex; Dabrin; Decan; Decilone; Dexamet; Dexticort; Drenex; Isodexam; Maxidex; Midexone†; Oradexon; Penodex; Santeson; Scancortin; Veramet; *Pol.*: Dexafree; Dexapolcort; Dexaven; Ozurdex; *Port.*: Decadron; Dexafree; Dexaval; Oradexon; Ozurdex; Ronic; *Rus.*: Detametazon (Детаметазон); Dexacort (Дексакорт); Dexafar (Дексафар); Dexamed (Дексамед); Dexapos (Дексапос); Dexason (Дексазон); Dexaven (Дексавен); Dexona (Дексона Д); Maxidex (Максидекс); Oftan Dexamethason (Офтан Дексаметазон); *S. Afr.*: Decadron†; Decasone; Dexagel; Dexona; Maxidex; Spersadex; *Singapore*: Decan; Decordex; Dexaltin; Dexamed; Dexasone; Dexmetha; Dextrasone; Eriadexone; Maxidex; Roximeth; SP-Cordexa; SW-Dexasone; *Spain*: Dexafree; Fortecortin; Maxidex; Ozurdex; *Swed.*: Dexacortal†; Isopto Maxidex; Opnol; Ozurdex; *Switz.*: Dexacortin†; Dexafree; Dexalocal; Fortecortin; Maxidex; Mephamesone; Ozurdex; Spersadex; *Thai.*: B Dexol; Decadron†; Dexa ANB; Dexa-O; Dexa-P; Dexa-Y; Dexa; Dexagel†; Dexaltin; Dexano; Dexapro; Dexasone; Dexion; Dexon; Dexone; Dexthasol; Dexthasone; Dexton; Lodexa; Oradexon; Phenodex; *Turk.*: Cebedex; Dekort; Deksalon; Deksamet; Dexa-Sine; Kordexa; Maxidex; Onadron; Spersadex; *UK*: Dexsol; Dropodex; Maxidex; Ozurdex; *Ukr.*: Dexagel (Дексагель)†; Farmadex (Фармадекс); Maxidex (Максидекс); Medexol (Медексол)†; Ozurdex (Озурдекс); *USA*: Aeroseb-Dex; Baycadron; Dalalone; Decadron†; Decaspray†; Dexasone; Dexone†; DexPak; Hexadrol†; Maxidex; Ozurdex; Zema; *Venez.*: Decalona; Decobel; Dexacort; Dexamin; Maradex.

Multi-ingredient Preparations. *Numerous preparations are listed in Volume B.*

Pharmacopoeial Preparations

BP 2014: Dexamethasone and Neomycin Ear Spray; Dexamethasone Eye Drops, Suspension; Dexamethasone Sodium Phosphate Eye Drops, Solution; Dexamethasone Sodium Phosphate Injection; Dexamethasone Sodium Phosphate Oral Solution; Dexamethasone Tablets;

USP 36: Ciprofloxacin and Dexamethasone Otic Suspension; Dexamethasone Acetate Injectable Suspension; Dexamethasone Elixir; Dexamethasone Gel; Dexamethasone Ophthalmic Suspension; Dexamethasone Oral Solution; Dexamethasone Sodium Phosphate Cream; Dexamethasone Sodium Phosphate Inhalation Aerosol; Dexamethasone Sodium Phosphate Injection; Dexamethasone Sodium Phosphate Ophthalmic Ointment; Dexamethasone Sodium Phosphate Ophthalmic Solution; Dexamethasone Tablets; Dexamethasone Topical Aerosol; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Dexamethasone Ophthalmic Suspension; Neomycin Sulfate and Dexamethasone Sodium Phosphate Cream; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate and Dexamethasone Sodium Phosphate Ophthalmic Solution; Tobramycin and Dexamethasone Ophthalmic Ointment; Tobramycin and Dexamethasone Ophthalmic Suspension.

Dichlorisone Acetate *(rINNM)* ⊗

Acetato de diclorisona; Dichlorisone, Acétate de; Dichlorisoni Acetas; Diclorisona, acetato de; Diclorisone Acetate; Дихлоризона Ацетат.

9α,11β-Dichloro-17α,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{23}H_{28}Cl_2O_5$=455.4

CAS — 7008-26-6 (dichlorisone); 79-61-8 (dichlorisone acetate).

UNII — 64FTA4579H.

Profile

Dichlorisone acetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.25 or 1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Dermaren; Dicloderm Forte†.

Diflorasone Diacetate *(BANM, USAN, rINNM)* ⊗

Diacetato de diflorasona; Diflorasona, diacetato de; Diflorasone, Diacétate de; Diflorasoni Diacetas; U-34865; Дифлоразона Диацетат.

6α,9α-Difluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-diacetate.

$C_{26}H_{32}F_2O_7$=494.5

CAS — 2557-49-5 (diflorasone); 33564-31-7 (diflorasone diacetate).

ATC — D07AC10.

ATC Vet — QD07AC10.

UNII — 7W2J095CWX.

Pharmacopoeias. In *US.*

USP 36: (Diflorasone Diacetate). A white to pale yellow, crystalline powder. Insoluble in water; soluble in acetone and in methyl alcohol; very slightly soluble in ether;

sparingly soluble in ethyl acetate; slightly soluble in toluene. Store in airtight containers.

Profile

Diflorasone diacetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Florone; *Gr.*: Florone; *India*: Diflorate; *Mex.*: Diasorane; *Spain*: Murode; *USA*: Apexi-Con; Florone; Maxiflor; Psorcon.

Multi-ingredient Preparations. *Arg.*: Filoderma Plus; Filoderma; Griseocrem.

Pharmacopoeial Preparations
USP 36: Diflorasone Diacetate Cream; Diflorasone Diacetate Ointment.

Diflucortolone *(BAN, USAN, rINN)* ⊗

Diflucortolona; Diflucortolonum; Diflukortolon; Diflukortoloni; Дифлукортолон.
6α,9α-Difluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.
$C_{22}H_{28}F_2O_4$=394.5
CAS — 2607-06-9.
ATC — D07AC06.
ATC Vet — QD07AC06; QD07XC04.
UNII — K253365DXI.

Diflucortolone Pivalate *(BANM, USAN, rINNM)* ⊗

Diflucortolona, pivalato de; Diflucortolone, Pivalate de; Diflucortoloni Pivalas; Pivalato de diflucortolona; SH-968; Дифлукортолона Пивалат.
Diflucortolone 21-pivalate.
$C_{27}H_{36}F_2O_5$=478.6
CAS — 15845-96-2.
ATC — D07AC06.
ATC Vet — QD07AC06.
UNII — ZR05N78276.

Diflucortolone Valerate *(BANM, rINNM)* ⊗

Diflucortolona, valerato de; Diflucortolone, Valérate de; Diflucortoloni Valeras; Diflukortolon Valerat; Valerato de diflucortolona; Дифлукортолона Валерат.
Diflucortolone 21-valerate.
$C_{27}H_{36}F_2O_5$=478.6
CAS — 59198-70-8.
ATC — D07AC06.
ATC Vet — QD07AC06.
UNII — 1A63Z067C8.

Pharmacopoeias. In *Br.*

BP 2014: (Diflucortolone Valerate). A white to creamy white crystalline powder. Practically insoluble in water; freely soluble in dichloromethane and in dioxan; sparingly soluble in ether; slightly soluble in methyl alcohol. Protect from light.

Profile

Diflucortolone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.1 or 0.3% of the valerate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nerisona; *Austria*: Neriforte; Nerisona; *Belg.*: Nerisona; *Braz.*: Nerisona; *Canad.*: Nerisone; *Fr.*: Nerisone; *Ger.*: Nerisona; *Gr.*: Nerisona; *Hong Kong*: Nerisone; *Indon.*: Nerilon; Nerisona; Valeron†; *Israel*: Neriderm; *Ital.*: Cortical; Dermaval; Dervin; Flu-Cortanest; Nerisona; Temetex; *Mex.*: Nerisona; *Neth.*: Nerisona; *NZ*: Nerisone; *Philipp.*: Nerisona; *Port.*: Nerisona; *S.Afr.*: Nerisone; *Spain*: Claral; *Turk.*: Temetex; *UK*: Nerisone.

Multi-ingredient Preparations. *Arg.*: Diflunazol; Nerisona C; Scheriderm; *Austria*: Travocort; *Belg.*: Travocort; *Braz.*: Bi-Nerisona; *Canad.*: Nerisalic†; *Chile*: Bi-Nerisona†; *Fr.*: Nerisalic; Nerisone C; *Ger.*: Travocort; *Gr.*: Nerisona C; Travocort; *Hong Kong*: Nerisone C; Travocort; *Indon.*: Nerisona Combi; Travocort; *Irl.*: Travocort; *Israel*: Isocort; Multiderm; Tevaderm; *Ital.*: Corti-Fluoral; Dermaflogil; Impetex; Nerisalic; Nerisona C; Travocort; *Malaysia*: Isoradin; Travocort; *Mex.*: Bi-Nerisona; Scheriderm; *NZ*: Nerisone C; *Philipp.*: Nerisona Combi; Travocort; *Pol.*: Travocort; *Port.*: Nerisona C; Travocort; *Rus.*: Travocort (Травокорт); *S.Afr.*: Maxaderm; Travocort; *Singapore*: Travocort; *Spain*: Claral Plus; *Switz.*: Travocort; *Thai.*: Travocort; *Turk.*: Impetex; Nerisona C; Travazol; Travocort; *Ukr.*: Travocort (Травокорт); *Venez.*: Binerisona.

Pharmacopoeial Preparations
BP 2014: Diflucortolone Cream; Diflucortolone Oily Cream; Diflucortolone Ointment.

Difluprednate *(USAN, rINN)* ⊗

CM-9155; Difluprednato; Difluprednatum; W-6309; Дифлупреднат.
6α,9α-Difluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate 17-butyrate.
$C_{27}H_{34}F_2O_7$=508.6
CAS — 23674-86-4.
ATC — D07AC19.
ATC Vet — QD07AC19.
UNII — S8A06QG2QE.

Profile

Difluprednate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or gel; concentrations used are 0.02 or 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Difluprednate is used topically as a 0.05% ophthalmic emulsion for the treatment of inflammation and pain following ocular surgery.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Epitopic; *Jpn*: Myser; *USA*: Durezol.

Fluclorolone Acetonide *(BAN, rINN)* ⊗

Acetónido de fluclorolona; Fluclorolona, acetónido de; Fluclorolone, Acétonide de; Fluclorolonl Acetonidum; Flucloronide (USAN); Fluklorolonacetonid; Fluklorolonіasetonidi; RS-2252; Флуклоролона Ацетонид.
9α,11β-Dichloro-6α-fluoro-21-hydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.
$C_{24}H_{29}Cl_2FO_5$=487.4
CAS — 3693-39-8.
ATC — D07AC02.
ATC Vet — QD07AC02.
UNII — MG258KTA37.

Profile

Fluclorolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.2%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Spain*: Cutanit.

Fludrocortisone Acetate

(BANM, rINNM) ⊗

Acetato de fludrocortisona; Fludrocortisona, acetato de; Fludrocortisonacetat; Fludrocortisone, acétate de; Fludrocortisoni Acetas; Fludrokortison acetát; Fludrokortisonacetat; Fludrokortisoniasetaatti; Fludrokortizon-acetát; Fludrokortizono acetatas; Fludrokortyzonu octan; 9α-Fluorohydrocortisone 21-Acetate; Флудрокортизона Ацетат.
9α-Fluoro-11β,17α,21-trihydroxypregn-4-ene-3,20-dione 21-acetate.
$C_{23}H_{31}FO_6$=422.5
CAS — 127-31-1 (fludrocortisone); 514-36-3 (fludrocortisone acetate).
ATC — H02AA02.
ATC Vet — QH02AA02.
UNII — V471F0PVH4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Fludrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol.

USP 36: (Fludrocortisone Acetate). White to pale yellow odourless or practically odourless, hygroscopic, crystals or crystalline powder. Insoluble in water; sparingly soluble in alcohol and in chloroform; slightly soluble in ether. Protect from light.

Uses and Administration

Fludrocortisone is a corticosteroid with glucocorticoid and highly potent mineralocorticoid activity (p. 1597.1).

Fludrocortisone acetate is given orally to provide mineralocorticoid replacement in primary adrenocortical insufficiency (p. 1600.2), with glucocorticoids. It is used in a dose range of 50 to 300 micrograms daily.

Fludrocortisone acetate may also be given with glucocorticoid therapy in doses of up to 200 micrograms daily in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2).

It is also given in the management of severe orthostatic hypotension (see below).

Fludrocortisone acetate is applied topically for its glucocorticoid actions in the treatment of various disorders. It is used as an ingredient of eye ointment or ear drops, usually in a concentration of 0.1%. Fludrocortisone acetate has also been included in topical preparations used for skin disorders. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Administration. A study of fludrocortisone requirements in 10 patients with Addison's disease indicated that dosage was often inadequate.[1] Nine were initially on fludrocortisone 50 to 100 micrograms daily in addition to cortisone or hydrocortisone; 5 were also taking levothyroxine for an associated auto-immune thyroid disease; one, who had detectable levels of aldosterone, was not initially receiving fludrocortisone. All the patients had evidence of sodium and water depletion and fludrocortisone was started at 300 micrograms daily, with downwards adjustments. Most patients required 200 micrograms daily; 2 patients elected to remain on 300 micrograms daily, but in most this dose caused pronounced sodium and water retention. The patient with detectable aldosterone levels required 50 micrograms daily. Eight of the 10 patients felt better on the higher fludrocortisone doses while 2 felt no change.

1. Smith SJ, *et al.* Evidence that patients with Addison's disease are undertreated with fludrocortisone. *Lancet* 1984; i: 11–14.

Neurally mediated hypotension. Fludrocortisone may be used in the management of neurally mediated hypotension in patients who require drug therapy (see p. 1277.2) but there is limited evidence to support its use.

Orthostatic hypotension. Orthostatic (postural) hypotension[1-5] is a fall in blood pressure that occurs upon rising abruptly to an erect position, although it may also occur after a period of prolonged standing. Characteristic symptoms include lightheadedness, dizziness, blurred vision, weakness in the limbs, and syncope.

The causes of orthostatic hypotension are wide-ranging and include autonomic dysfunction, such as in the Shy-Drager syndrome, diabetes mellitus, and Parkinson's disease, circulating volume depletion, phaeochromocytoma, and Addison's disease. Orthostatic hypotension may also occur following a period of prolonged bed rest or after meals.

Orthostatic hypotension may result from the adverse effects of a range of drugs, such as antihypertensives, diuretics, tricyclic antidepressants, phenothiazines, and MAOIs.

In mild cases **nonpharmacological treatment** alone may be adequate. This includes increasing salt intake if not contra-indicated, maintaining adequate hydration, the use

of elastic stockings to improve venous return and increase cardiac output, and elevating the head of the bed to reduce early morning symptoms. Drug-induced orthostatic hypotension should be treated by withdrawing the drug or by dose reduction.

Pharmacological treatment. No pharmacological treatment is entirely satisfactory: responses and tolerance vary greatly between patients. Fludrocortisone acetate is usually tried first; it increases sodium retention and thus plasma volume. Most reports indicate some response in about 80% of patients, but hypokalaemia, fluid retention, and supine hypertension may limit its use. In patients who fail to respond adequately an NSAID (usually indometacin) may be tried, alone or with fludrocortisone. In patients with overt autonomic failure a beta blocker with some partial agonist activity, such as pindolol, may be tried although they are potentially dangerous.

Sympathomimetics may be useful in some patients with autonomic failure; the direct acting drugs such as phenylephrine or midodrine are usually more consistently effective than the indirect such as ephedrine, but even so, responses tend to vary with the degree of denervation. Ambulatory noradrenaline infusion therapy is under investigation for severe refractory orthostatic hypotension. Patients with central neurological abnormalities may respond to desmopressin, while drugs such as ergotamine or dihydroergotamine may be useful for resistant disease.

Other drugs that have been tried include metoclopramide, which may be useful for autonomic symptoms in patients with diabetes mellitus, fluoxetine, octreotide, yohimbine, clonidine, and in patients with concurrent anaemia, erythropoietin. Caffeine has been tried in postprandial hypotension but its value in all but the mildest cases is dubious.[3] The use of MAOIs (which given alone can induce orthostatic hypotension) with a sympathomimetic to induce a pressor reaction is controversial. Most of these drugs have potentially serious adverse effects and few are well evaluated.

1. Ahmad RAS, Watson RDS. Treatment of postural hypotension: a review. *Drugs* 1990; 39: 74–85.
2. Tonkin AL, Wing LMH. Hypotension: assessment and management. *Med J Aust* 1990; 153: 474–85.
3. Schoenberger JA. Drug-induced orthostatic hypotension. *Drug Safety* 1991; 6: 402–7.
4. Stumpf JL, Mitrzyk B. Management of orthostatic hypotension. *Am J Hosp Pharm* 1994; 51: 648–60.
5. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; 35: 124–32.
6. Frishman WH, *et al.* Drug treatment of orthostatic hypotension and vasovagal syncope. *Heart Dis* 2003; 5: 49–64.
7. Freeman R. Treatment of orthostatic hypotension. *Semin Neurol* 2003; 23: 435–42.
8. Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007; 120: 841–7.

Adverse Effects, Treatment, Withdrawal, and Precautions

Fludrocortisone acetate has glucocorticoid actions about 10 times as potent as hydrocortisone and mineralocorticoid effects more than 100 times as potent. Adverse effects are mainly those due to mineralocorticoid activity, as described on p. 1615.3. Withdrawal effects of corticosteroids and precautions for their use are discussed on p. 1618.1 and p. 1618.3, respectively.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fludrocortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Fludrocortisone is readily absorbed from the gastrointestinal tract. The plasma half-life is about 3.5 hours or more, but fludrocortisone has a more prolonged biological half-life of 18 to 36 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lonikan; *Austral.*: Florinef; *Austria*: Astonin H; *Braz.*: Florinefe; *Canad.*: Florinef; *Chile*: Florinef; *Denm.*: Florinef; *Fin.*: Florinef; *Fr.*: Adixone; *Ger.*: Astonin H; *Gr.*: Florinef; *Hong Kong*: Florinef; *Hung.*: Astonin H; *India*: Floricot; *Irl.*: Florinef; *Malaysia*: Florinef; *Mex.*: Florinef; *Neth.*: Florinef; *Norw.*: Florinef; *NZ*: Florinef; *Pol.*: Cortineff; *Rus.*: Cortineff (Кортинефф); *S.Afr.*: Florinef; *Singapore*: Florinef; *Spain*: Astonin; *Swed.*: Florinef; *Switz.*: Florinef; *Thai.*: Florinef; *UK*: Florinef; *Ukr.*: Cortineff (Кортинефф); *USA*: Florinef.

Multi-ingredient Preparations. *Belg.*: Panotile; *Braz.*: Panotil; *Fr.*: Panotile; *Gr.*: Paroticin; *Indon.*: Nelicort; Otilon; Otopain; Otopraf; *Neth.*: Panotile; *Pol.*: Dicortineff; *Spain*: Fludroneft; Panotile†; *Switz.*: Panotile; *Thai.*: Otosamthong†; SM Oto.

Pharmacopoeial Preparations
BP 2014: Fludrocortisone Tablets;
USP 36: Fludrocortisone Acetate Tablets.

Fludroxycortide (BAN, rINN) ⊗

33379; Fludroksikortidi; Fludroxicortida; Fludroxikortid; Fludroxycortidum; Fluorandrenolone; 6α-Fluoro-16α-hydroxyhydrocortisone 16,17-Acetonide; Flurandrenolide (USAN); Flurandrénolone; Флудроксикортид.

6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

$C_{24}H_{33}FO_6$=436.5

CAS — 1524-88-5.

ATC — D07AC07.

ATC Vet — QD07AC07.

UNII — 8EUL29XUQT.

Pharmacopoeias. In *US*.

USP 36: (Flurandrenolide). A white to off-white, fluffy, odourless, crystalline powder. Practically insoluble in water and in ether; soluble 1 in 72 of alcohol, 1 in 10 of chloroform, and 1 in 25 of methyl alcohol. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Profile

Fludroxycortide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, lotion, or ointment containing 0.0125% or 0.05%. It is also used as an adhesive polyethylene tape impregnated with fludroxycortide 4 micrograms/cm².

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Drenison; *UK*: Haelan; *USA*: Cordran.

Multi-ingredient Preparations. *Braz.*: Dreniformio; Drenison N.

Pharmacopoeial Preparations
USP 36: Flurandrenolide Cream; Flurandrenolide Lotion; Flurandrenolide Ointment; Flurandrenolide Tape; Neomycin Sulfate and Flurandrenolide Cream; Neomycin Sulfate and Flurandrenolide Lotion; Neomycin Sulfate and Flurandrenolide Ointment.

Flumetasone Pivalate (BANM, rINNM) ⊗

Flumetason pivalát; Flumetasona, pivalato de; Flumétasone, Pivalate de; Flumetasoni Pivalas; Flumetasonipivalaatti; Flumetasonpivalat; Flumetasonum Pivalas; Flumetazon Pivalat; Flumetazono pivalatas; Flumetazon-pivalát; Flumetazonu piwalan; Flumethasone Pivalate (USAN); Flumethasone Trimethylacetate; NSC-107680; Pivalato de flumetasona; Флуметазона Пивалат.

Flumethasone 21-pivalate.

$C_{27}H_{36}F_2O_6$=494.6

CAS — 2002-29-1.

ATC — D07AB03.

ATC Vet — QD07AB03.

UNII — 0DV09X6F21.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Flumetasone Pivalate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane; sparingly soluble in acetone. Protect from light.

USP 36: (Flumethasone Pivalate). A white to off-white crystalline powder. Insoluble in water; soluble 1 in 89 of alcohol, 1 in 350 of chloroform, and 1 in 2800 of ether; slightly soluble in methyl alcohol; very slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Flumetasone pivalate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.02% cream, ointment, or lotion. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Flumetasone pivalate is also used in ear drops in a concentration of 0.02% with clioquinol 1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Locacortene; *Ger.*: Cerson; Locacorten; *Gr.*: Locacorten; *Neth.*: Locacorten; *Pol.*: Lorinden†; *Switz.*: Locacorten.

Multi-ingredient Preparations. *Arg.*: Tresite F; *Austral.*: Locacorten Vioform; *Belg.*: Locasalen; *Braz.*: Locorten Vioformio; Losalen; *Canad.*: Locacorten Vioform; *Denm.*: Locacorten Vioform; *Fin.*: Locacorten Vioform; *Fr.*: Alkocortenbioform†; Alkosalen†; Alkotar†; Locacortene Vioforme†; Locasalene†; Psocortene†; *Ger.*: DuoGalen; Locacorten Vioform; Locasalen; *Gr.*: Locacorten Taz; Locacorten Vioform; Locacorten with Neomycin; Locasalene; *Hong Kong*: Locasalen; *Hung.*: Lorinden A; Lorinden C; *Indon.*: Locasalen; *Israel*: Topisalen; *Ital.*: Locorten Vioformio†; Locorten; Locorten; Losalen; Vasosterone Oto†; *Neth.*: Locacorten Vioform; Locasalen; *NZ*: Locacorten Vioform; Locorten Vioform; *Philipp.*: Locasalen; *Pol.*: Lorinden A; Lorinden C; Lorinden N; *Rus.*: Lorinden A (Лориден А); Lorinden C (Лориден С); *S.Afr.*: Locacorten Vioform; *Spain*: Losalen†; *Swed.*: Locacorten Vioform; *Switz.*: Locasalen; *Thai.*: Flumasalen†; Locasalen; *Turk.*: Locacortene Vioform; Locasalene; *UK*: Locorten Vioform; *Ukr.*: Lorinden A (Лориден А); Lorinden C (Лориден С); *Venez.*: Locasalen; Locorten Vioformo.

Pharmacopoeial Preparations
USP 36: Flumethasone Pivalate Cream.

Flunisolide (BAN, USAN, rINN) ⊗

Flunisolid; Flunisolida; Flunisolidi; Flunisolidum; RS-1320 (flunisolide acetate); RS-3999; Флунизолид.

6α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{31}FO_6$=434.5

CAS — 3385-03-3 (flunisolide); 77326-96-6 (flunisolide hemihydrate); 4533-89-5 (flunisolide acetate).

ATC — R01AD04; R03BA03.

ATC Vet — QR01AD04; QR03BA03.

UNII — QK4DYS664X.

Pharmacopoeias. In *US* which specifies the hemihydrate.

USP 36: (Flunisolide). A white to creamy-white crystalline powder. Practically insoluble in water; soluble in acetone; sparingly soluble in chloroform; slightly soluble in methyl alcohol.

Uses and Administration

Flunisolide is a corticosteroid with glucocorticoid activity (p. 1597.1) used as a nasal spray for the prophylaxis and treatment of allergic **rhinitis** (p. 612.1). In the UK a formulation containing 25 micrograms per metered spray is available; in the USA each metered spray of some preparations contains 29 micrograms flunisolide hemihydrate. The recommended starting dose is 2 sprays into each nostril twice daily, increased if necessary to three times daily, and then reduced for maintenance. In the USA a maximum dose of 8 sprays into each nostril daily has been established.

Like some other corticosteroids, flunisolide is also used by inhalation from metered-dose aerosols in the management of **asthma** (see p. 1600.3). The usual dosage of flunisolide from an aerosol using chlorofluorocarbon (CFC) propellants is 500 micrograms inhaled twice daily. In severe asthma the dosage may be increased but should not exceed a total of 2 mg daily. A hydrofluoroalkane (CFC-free) aerosol, which is also available in some countries, has a lower dose because of different delivery characteristics. The usual dose, expressed as flunisolide hemihydrate, is

160 micrograms twice daily, which may be increased after 3 to 4 weeks but should not exceed 320 micrograms twice daily.

For doses used in children, see below.

Administration in children. Flunisolide may be used in children as a nasal spray for the prophylaxis and treatment of allergic rhinitis. In the UK a formulation containing 25 micrograms per metered spray is available; in the USA each metered spray of some preparations contains 29 micrograms flunisolide hemihydrate. In the UK, for children aged from 5 to 14 years, a starting dose of 1 spray into each nostril may be given up to a maximum of 3 times daily. Children in the USA aged 6 to 14 years old may be treated with this dose, or an initial 2 sprays into each nostril twice daily (which is also the recommended maximum of 4 sprays into each nostril daily).

Flunisolide is also used by inhalation from metered-dose aerosols in the management of asthma in children. The dosage of flunisolide from an aerosol using chlorofluorocarbon (CFC) propellants for children of 6 to 15 years of age is 500 micrograms inhaled twice daily, which should not be exceeded. A hydrofluoroalkane (CFC-free) aerosol, which is also available in some countries, has a lower dose because of different delivery characteristics. In children aged 6 to 11 years of age a dose of flunisolide hemihydrate 80 micrograms twice daily may be used, increased after 3 to 4 weeks to a maximum of 160 micrograms twice daily if necessary.

For both indications, the dose should be reduced to the lowest effective for maintenance. Older children may be given adult doses (see p. 1635.3).

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Flunisolide is reported to undergo extensive first-pass metabolism, with only 20% of the dose available systemically if it is given orally. The major metabolite, 6β-hydroxyflunisolide has some glucocorticoid activity; it has a half-life of about 4 hours. Only small amounts of flunisolide are absorbed after intranasal doses.

References.
1. Chaplin MD, *et al.* Flunisolide metabolism and dynamics of a metabolite. *Clin Pharmacol Ther* 1980; 27: 402–13.
2. Möllmann H, *et al.* Pharmacokinetic/pharmacodynamic evaluation of systemic effects of flunisolide after inhalation. *J Clin Pharmacol* 1997; 37: 893–903.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Syntaris†; *Canad.*: Rhinalar; *Cz.*: Syntaris†; *Fr.*: Nasalide†; *Ger.*: Syntaris; *Gr.*: Bronalide; *Ital.*: Aerflu; Aerolid; Asmaflu; Assolid; Careflu; Charlyn; Citiflux; Desaflu; Doricoflu; Eliosid; Euroflu; Fluminex; Flunitop; Forbest; Givair; Inalcort†; Kaimil; Levonis; Lunibron; Lunis; Multinebulgen; Nambrol; Nebulcort; Nebulgen; Nereflun; Nisolid; Nisoran; Plaudit; Pulmist; saflineb; Syntaris; Turm; Ventoflu; *Neth.*: Syntaris†; *Norw.*: Lokilan†; *UK*: Syntaris; *USA*: AeroBid; AeroSpan; Nasarel.

Multi-ingredient Preparations. *Ital.*: Plenaer.

Pharmacopoeial Preparations
USP 36: Flunisolide Nasal Solution.

Fluocinolone Acetonide *(BANM, USAN, rINN)* ⊗

Acetónido de fluocinolona; 6α,9α-Difluoro-16α-hydroxyprednisolone Acetonide; Fluocinolon acetonid; Fluocinolona, acetónido de; Fluocinolon-acetonid; Fluocinolonacetonid; Fluocinolone, acétonide de; Fluocinoloni Acetonidum; Fluocinolono acetonidas; Fluocynolonu acetonid; Fluosinoloniasetonidi; NSC-92339; Флуоцинолона Ацетонид.

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.

$C_{24}H_{30}F_2O_6$=452.5

CAS — 67-73-2.

ATC — C05AA10; D07AC04; S01BA15; S02BA08.

ATC Vet — QC05AA10; QD07AC04; QS01BA15; QS02BA08.

UNII — QCD5FD6S2M.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet.* Br. and *Viet.* have a separate monograph for the dihydrate; *US* allows either the anhydrous form or the dihydrate.

Ph. Eur. 8: (Fluocinolone Acetonide). A white or almost white, crystalline powder. It exhibits polymorphism. Practically insoluble in water; soluble in dehydrated alcohol and in acetone. Protect from light.

BP 2014: (Fluocinolone Acetonide Dihydrate). A white or almost white, crystalline powder. Practically insoluble in water and in hexane; soluble in dehydrated alcohol; freely soluble in acetone; sparingly soluble in dichloromethane and in methyl alcohol. Protect from light.

USP 36: (Fluocinolone Acetonide). It is anhydrous or contains two molecules of water of hydration. A white or practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 45 of alcohol, 1 in 25 of chloroform, and 1 in 350 of ether; soluble in methyl alcohol.

Profile

Fluocinolone acetonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application; concentrations normally range from 0.0025 to 0.025% although higher-strength preparations may be available. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocinolone acetonide is also used topically with an antibacterial in the treatment of infective inflammatory eye, ear, and nose disorders. Ear drops containing fluocinolone acetonide 0.01% may be used in eczematous external otitis. A sterile implant of fluocinolone acetonide is used intravitreally for the treatment of chronic non-infectious posterior uveitis. Another intravitreal implant is used in the treatment of diabetic macular oedema, and is under investigation in age-related macular degeneration and retinal vein occlusion. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

References.
1. Mohammad DA, *et al.* Retisert: is the new advance in treatment of uveitis a good one? *Ann Pharmacother* 2007; 41: 449–54.
2. Sanford M. Fluocinolone acetonide intravitreal implant (Iluvien): in diabetic macular oedema. *Drugs* 2013; 73: 187–93.
3. Haritoglou C, *et al.* Fluocinolone acetonide and its potential in the treatment of chronic diabetic macular edema. *Clin Ophthalmol* 2013; 7: 503–9.

Formulation. The potency of fluocinolone acetonide varied with the formulation in a study[1] involving different *Synalar* topical preparations, the gel, ointment, and cream. The cream was the most potent followed by the gel, and then the ointment. A comparison of topical vasoconstrictor activity (used as an index of potency) unexpectedly found that the commercial dilutions of the cream (containing 0.00625% and 0.0025%) were indistinguishable in their effects from the full-strength (0.025%) cream.

1. Gao HY, Li Wan Po A. Topical formulations of fluocinolone acetonide: are creams, gels and ointments bioequivalent and does dilution affect activity? *Eur J Clin Pharmacol* 1994; 46: 71–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluocinolone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Duoflu; Flulone; *Belg.*: Synalar†; *Canad.*: Capex; Derma-Smoothe/FS; DermOtic; Fluoderm; Synalar; *Chile*: Adermina; *Cz.*: Flucinar; Gelargin; *Denm.*: Synalar; *Fr.*: Synalar†; *Ger.*: Flucinar; Jellin; *Gr.*: Synalar Simple; *Hong Kong*: Aplosyn†; Synaderm†; Synalar; Synalone†; Synfulin†; Uni-Fluocin†; *Hung.*: Flucinar; *India*: Emderm; Fludin; Flucocin; Flucort-H; Flucort; Luci; *Indon.*: Cinolon; Dermasolon; Esinol; Inoderm; Licosolon; *Israel*: Dermalar†; *Ital.*: Dermolin; Fluocit†; Fluomix Same; Fluovitel; Localyn SV†; Localyn; Omniderm; Sterolone; Ultraderm; *Malaysia*: Fluciderm; *Mex.*: Cortifung-S; Cortilona; Cremisona; Farmacorti; Flumicin†; Fluomex; Fusalar†; Lonason; Naflucen; Synalar; *Norw.*: Synalar; *NZ*: Synalar; *Philipp.*: Aplosyn; Cynozet; Fludin; Synalar; Syntopic; *Pol.*: Flucinar; *Port.*: Oto-Synalar N; Synalar; *Rus.*: Flucinar (Флуцинар); Sinaflan (Синафлан); Sinoderm (Синодерм); *S.Afr.*: Cortoderm; Fluoderm†; Synalar; *Singapore*: Fluciderm; Flunolone-V; Synalar; Synfulin; *Spain*: Co Fluocin Fuerte†; Cortiespec†; Fluocid Forte†; Fluodermo Fuerte†; Flusolgen†; Gelidina; Synalar Rectal Simple; Synalar; *Swed.*: Synalar; *Switz.*: Synalar; *Thai.*: Cervicum†; Flunolone-V†; Fulone†; Supralan†; Synalar†; *UK*: Iluvien; Synalar; *Ukr.*: Flucar (Флуцар); Flucinar (Флуцинар); Synaflan (Синафлан); *USA*: Capex; Derma-Smoothe/FS; DermOtic; Fluonid; Retisert Synalar; Synemol; *Venez.*: Bratofil; Neo-Synalar.

Multi-ingredient Preparations. *Arg.*: Neoblanc Tri-Luma; Trimegtante; *Belg.*: Procto-Synalar; Synalar Bi-Otic; *Braz.*: Dermoxin†; Elotin; Fluo-Vaso; Hormoskin; Neocinolon; Otomixyn Otosynalar; Suavicid; Tri-Luma; Triderm; Vitacid Plus; *Chile*: Otoseptil; Tri-Luma; *Denm.*: Synalar med Chinoform; *Fin.* Cetraxal Comp; *Fr.*: Antibio-Synalar; *Ger.*: Jellin-Neomycin *Gr.*: Myco-Synalar; Otospon; Procto Synalar-N; Procto-Synala N; Synalar; *Hong Kong*: Aplosyn-C†; Aplosyn-N†; Aplosyn Otic; Flunolone; Fluonid-N; Fusodic†; Synaderm-N†; Synala N; Synalone-N†; Synco-CFN†; Syneolona†; Tri-Luma; *Hung.* Flucinar N; *India*: Atderm; Ceflox-CF; Ciprobiotic-FC; Ciprolar F; Ciprolar-FC; E-Derm; Eczo-Wokadine; Flual-M; Flucocin-N Flucocip; Flucort-C; Flucort-MZ; Flucort-N; Flucreme-NM Fungitop-F; Gentacort-FC; Gentacort-MF; GMP; Luci-N; Medir on; Micogel F; Mictop-F; Nazo-F; Neocip FC; Olamin-F; Zole-F *Indon.*: Bravoderm-N; Cinogenta; Cinolon-N; Fasolon; Fluo cort-N; Genolon; Gentasolon; Kalcinol-N; Neosinol; Ocidерm-N Refaquin; Sinobiotik†; Synalten; Zumaderm-N†; *Ital.*: Cortan est Plus; Doricum; Lauromicina; Localyn-Neomicina; Localyn Localyn; Mecloderm F; Nefluan; Proctolyn; *Malaysia*: Flumi cin†; Tri-Luma; *Mex.*: Acenil; Bentix; Cetoquina Y; Cortifung N; Cortifung-Y; Cortilona Compuesta; Dermatofin; Farmacort YC; Fluccinol N; Fluo Grin†; Gynoclin-V; Lasalar-Y; Luzolon Y; Neoderm-F; Nysmosons-V; Promibasol-Plus†; Synalar C Synalar N; Synalar Neo; Synalar O; Synalar Oftalmico†; Tri Luma; Vagitrol-V; Yderm; *Neth.*: Synalar; *Norw.*: Synalar mec Chinoform; *Philipp.*: Aceflo; Aplosyn C; Aplosyn N; Aplosyn Otic; Neo-Synalar; Synalar Otic; Tri-Luma; *Pol.*: Flucinar N *Port.*: Synalar N; Synalar Rectal; *Rus.*: Flucinar N (Флуцинар H); Nefluan (Нефлуан); Simetrid (Симетрид); *S.Afr.*: Cortoderm-C†; Synalar C; Synalar N; *Singapore*: Flunolone; Syneolona; Tri-Luma; *Spain*: Abrasone Rectal; Abrasone; Aceotc Plus; Alergical; Artrodesmol Extra; Cetraxal Plus; Creanolona Flodermol; Midacina; Otomidrin; Synalar Nasal; Synalar Otico Synalar Rectal; Synalotic; Ultramicina Plus; Vinciseptil Otico *Switz.*: Procto-Synalar N; Synalar N; *Thai.*: Flunobate-N; Flunolone; Fluo-Neo; Fluocort-N; Fluonid-N†; Gental-F; Supralan-N; Synalar N; Tri-Luma; *UK*: Synalar C; Synalar N; *Ukr.* Cetraxal Plus (Цетраксал Плюс); Flucinar N (Флуцинар N). *USA*: Tri-Luma; *Venez.*: Bratofil c Neomicina; Neo-Synalar cor Neomicina; Tri-Luma.

Pharmacopoeial Preparations
BP 2014: Fluocinolone Cream; Fluocinolone Ointment;
USP 36: Fluocinolone Acetonide Cream; Fluocinolone Acetonide Ointment; Fluocinolone Acetonide Topical Solution; Neomycin Sulfate and Fluocinolone Acetonide Cream.

Fluocinonide *(BAN, USAN, rINN)* ⊗

Fluocinolide; Fluocinolone Acetonide 21-Acetate; Fluocinonid; Fluocinónida; Fluocinonidum; Fluosinonidi; NSC-101791; Флуоциноníд.

6α,9α-Difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{26}H_{32}F_2O_7$=494.5

CAS — 356-12-7.

ATC — C05AA11; D07AC08.

ATC Vet — QC05AA11; QD07AC08.

UNII — 2W4A77YPAN.

Pharmacopoeias. In *Br., Chin., Jpn*, and *US.*

BP 2014: (Fluocinonide). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in chloroform. Protect from light.

USP 36: (Fluocinonide). A white to cream-coloured, crystalline powder having not more than a slight odour. Practically insoluble in water; slightly soluble in alcohol, in methyl alcohol, and in dioxan; sparingly soluble in acetone and in chloroform; very slightly soluble in ether.

Profile

Fluocinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream, gel, lotion, ointment, or scalp application containing 0.05%. A cream containing 0.1% may also be available.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Lidemol; Lidex; Lyderm; Tiamol; Topactin†; Topsyn†; *Denm.*: Metosyn; *Ger.*: Topsym; *Gr.*: Lamagramm; Lidex; *Ital.*: Flu-21; Topsyn; *Mex.*: Topsyn;

Norw.: Metosyn; *Philipp.*: Dermadex; Lidemol; Lidex; *Spain*: Novoter; *Switz.*: Topsym; *UK*: Metosyn; *USA*: Lidex; Vanos.

Multi-ingredient Preparations. *Ger.*: Jelliproct; *Israel*: Comagis; *Mex.*: Topsyn-Y; *Philipp.*: Lidex NGN; *Spain*: Novoter Gentamicina; *Switz.*: Mycolog N; Topsym polyvalent; *UK*: Vipsogal; *Ukr.*: Cremgen (Кремген).

Pharmacopoeial Preparations
BP 2014: Fluocinonide Cream; Fluocinonide Ointment;
USP 36: Fluocinonide Cream; Fluocinonide Gel; Fluocinonide Ointment; Fluocinonide Topical Solution.

Fluocortin Butyl *(BAN, USAN, rINNM)* ⊗

Butil éster de la fluocortina; Butylis Fluocortinas; Fluocortina, butil éster de la; Fluocortine Butyle; SH-K-203; Флуокортин бутил.

Butyl 6α-fluoro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-21-oate.

$C_{26}H_{35}FO_5$=446.6

CAS — 33124-50-4 (fluocortin); 41767-29-7 (fluocortin butyl).

ATC — D07AB04.

ATC Vet — QD07AB04.

UNII — 6N7OA9MO7O.

Profile

Fluocortin butyl is a corticosteroid that has been used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.75%. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocortin butyl has also been used in the form of a dry powder nasal inhalation for the management of allergic rhinitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Vaspit; *Spain*: Vaspit.

Fluocortolone *(BAN, USAN, rINN)* ⊗

Fluocortolona; Fluocortolonum; Fluokortolon; Fluokortoloni; 6α-Fluoro-16α-methyl-1-dehydrocorticosterone; SH-742; Флуокортолон.

6α-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 152-97-6.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

UNII — 65VXC1MH0J.

Fluocortolone Caproate *(USAN, rINNM)* ⊗

Caproato de fluocortolona; Fluocortolona, caproato de; Fluocortolone, Caproate de; Fluocortolone Hexanoate (BANM); Fluocortoloni Caproas; Fluokortolon Kaproat; Fluokortolon Kapronat; SH-770; Флуокортолона капроат.

Fluocortolone 21-hexanoate.

$C_{28}H_{39}FO_5$=474.6

CAS — 303-40-2.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

UNII — 90893P8662.

Pharmacopoeias. In *Br.*

BP 2014: (Fluocortolone Hexanoate). A white or creamy-white, odourless or almost odourless, crystalline powder. It exhibits polymorphism. Practically insoluble in water and in ether; very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone and in dioxan; sparingly soluble in chloroform. Protect from light.

Fluocortolone Pivalate *(BANM, rINNM)* ⊗

Fluocortolona, pivalato de; Fluocortolone, Pivalate de; Fluocortolone Trimethylacetate; Fluocortoloni Pivalas; Fluokortolon Pivalat; Fluokortolonipivalaatti; Fluokortolono pivalatas; Fluokortolonpivalat; Fluokortolon-pivalát; Pivalato de fluocortolona; Флуокортолона пивалат.

Fluocortolone 21-pivalate.

$C_{27}H_{37}FO_5$=460.6

CAS — 29205-06-9.

ATC — C05AA08; D07AC05; H02AB03.

ATC Vet — QC05AA08; QD07AC05; QH02AB03.

UNII — 9J8AL6K50Q.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Fluocortolone Pivalate). A white or almost white crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane and in dioxan. Protect from light.

Profile

Fluocortolone and its esters are corticosteroids mainly used topically for their glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. They are usually used as a cream or ointment; concentrations usually used are 0.25% of the caproate with 0.25% of either the free alcohol or pivalate ester. The pivalate and caproate esters have also been used together in ointments or suppositories for the treatment of anorectal disorders.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Fluocortolone free alcohol is sometimes given orally for its systemic effects in conditions for which corticosteroids are indicated (p. 1597.3), in usual doses of 5 to 100 mg daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ultracur S; *Austria*: Ultralan; Ultralan; *Ger.*: Ultralan; *Gr.*: Imiprom†; Ultralanum; *Hong Kong*: Ultralan; *Israel*: Ultralan; *Ital.*: Ultralan; Ultralan; *Philipp.*: Ultralan†; *Spain*: Ultralan M; *Turk.*: Ultralan; Ultralan; *UK*: Ultralanum Plain.

Multi-ingredient Preparations. *Arg.*: Ultraproct; *Austral.*: Ultraproct†; *Austria*: Doloproct; Pilison; *Belg.*: Doloproct; Ultraproct; *Braz.*: Ultraproct; *Chile*: Ultraproct; *Denm.*: Doloproct; Doloproct; *Fin.*: Neoproct; *Fr.*: Ultralan†; Ultraproct; *Ger.*: Doloproct; *Gr.*: Doloproct; *Hong Kong*: Ultraproct N; *Hung.*: Doloproct; *Indon.*: Ultraproct N; Ultraproct†; *Irl.*: Ultraproct; *Ital.*: Doloproct; Ultraproct; *Mex.*: Ultraproct; *NZ*: Doloproct; Ultraproct; *Philipp.*: Doloproct; Ultraproct; *Port.*: Ultraproct; *Rus.*: Doloprokt (Долопрокт); Ultraproct (Ультрапрокт); *Spain*: Doloproct; *Swed.*: Doloproct; *Thai.*: Scheriproct N; *Turk.*: Doloproct; Ultralan Crinale; Ultraproct; *UK*: Ultraproct; *Ukr.*: Doloproct (Долопрокт); Ultraproct (Ультрапрокт).

Pharmacopoeial Preparations
BP 2014: Fluocortolone Cream.

Fluorometholone *(BAN, rINN)* ⊗

Fluorométholone; Fluorometholonum; Fluorometolon; Fluorometolona; Fluorometoloni; Флуорометолон.

9α-Fluoro-11β,17α-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{29}FO_4$=376.5

CAS — 426-13-1.

ATC — C05AA06; D07AB06; S01BA07.

ATC Vet — QC05AA06; QD07AB06; QD07XB04; QD10AA01; QS01BA07; QS01CB05.

UNII — SV0CSG527L.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Fluorometholone). A white to yellowish white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in ether.

USP 36: (Fluorometholone). A white to yellowish-white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 200 of alcohol and 1 in 2200 of chloroform; very slightly soluble in ether. Store in airtight containers. Protect from light.

Fluorometholone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de fluorometolona; Fluorométholone, Acétate de; Fluorometholoni Acetas; Fluorometolon Asetat; Fluorometolona, acetato de; U-17323; Флуорометолона ацетат.

Fluorometholone 17-acetate.

$C_{24}H_{31}FO_5$=418.5

CAS — 3801-06-7.

ATC — C05AA06; D07AB06; S01BA07.

ATC Vet — QC05AA06; QD07AB06; QS01BA07.

UNII — 9I50C3I3OK.

Pharmacopoeias. In *US*.

USP 36: (Fluorometholone Acetate).

Profile

Fluorometholone is a corticosteroid used for its glucocorticoid activity (p. 1597.1), usually as eye drops containing 0.1%, in the treatment of allergic and inflammatory conditions of the eye. Fluorometholone acetate is used similarly.

Fluorometholone is also used topically in the treatment of various skin disorders.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function. When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Flarex; FML; *Austral.*: Flarex; Flucon; FML; *Belg.*: Fluacort; Flucon; FML; *Braz.*: Florate; Flumex; Flutinol; *Canad.*: Flarex; FML; *Chile*: Aflarex; Fluforte; Flumetol N; *China*: Flarex (擒雷); Flumetholon (氟美童); FML (艾氟龙); *Cz.*: Efflumidex; Flarex; Flucon; Fluoropos; *Denm.*: Flurolon; *Fin.*: FML; *Fr.*: Flucon; *Ger.*: Efflumidex; Fluoro-Ophtal†; Fluoropos; *Gr.*: Pacocinerin; Florate; Flucon; Fluxinam; FML; Talirax; Toscacort; *Hong Kong*: Flarex; Flucon†; Flumetholon; FML; *Hung.*: Efflumidex; Flarex†; Flucon; *India*: F-Lone; Flarex; Flomex; Flomon; Flosef; Flurisone; FML; FML; Mep-Fluron; *Indon.*: Flumetholon; Oculfam; *Irl.*: FML; *Israel*: Flarex; FML; *Ital.*: Flarex; Fluaton; Flumetol; *Malaysia*: Flarex; FML; *Mex.*: Flarex; Fluforte; Flumetol NF; *Neth.*: FML; *NZ*: Flucon; FML; *Philipp.*: Flarex; Flulon; FML; *Pol.*: Flarex; Flucon; *Port.*: Flurop; FML; *Rus.*: Flarex (Флярекс); *S.Afr.*: Flucon; FML; *Singapore*: FML; *Spain*: FML; Isopto Flucon; *Switz.*: FML; *Thai.*: Flarex; Flu Oph; Flucon; FML; *Turk.*: Flarex; Fluoropos; FML; *UK*: FML; *USA*: Eflone; Flarex; FML; *Venez.*: Aflarex; Flumetol.

Multi-ingredient Preparations. *Arg.*: Dellsan; Efemolina; FML Neo; Larsimal; Nesbiler; *Belg.*: Infectoflam†; *Braz.*: Flumex N; *Canad.*: FML Neo†; *China*: Infectoflam (易妥芬); *Ger.*: Cibaflam†; Efemolin†; *Gr.*: Efemoline; Fluorocort; FML Neo; Helpometil; Indo-Cort; Luzin; *Hong Kong*: Efemoline; *India*: Flomex N; FML Neo; FML-T; LT-Cin; Nutob-F; Obra-F; *Irl.*: FML Neo†; *Ital.*: Efemoline; Flumecidina†; Flumezina; Gentacort†; *Mex.*: Fluforte N; Fluorometil; *Philipp.*: Efemoline; Infectoflam; *Port.*: FML Neo; *S.Afr.*: Efemoline; FML Neo; *Singapore*: Efemoline; Infectoflam; *Spain*: Bexicortil†; Cortisdin Urea†; Flugen†; Fluorvas; *Switz.*: Efemoline; FML Neo; Infectoflam†; *Thai.*: Efemoline; FML Neo; Infectoflam†; *Turk.*: Efemoline; Flumetol†; *USA*: FML-S†.

Pharmacopoeial Preparations
BP 2014: Fluorometholone Eye Drops;
USP 36: Fluorometholone Cream; Fluorometholone Ophthalmic Suspension; Neomycin Sulfate and Fluorometholone Ointment; Tobramycin and Fluorometholone Acetate Ophthalmic Suspension.

Fluprednidene Acetate *(BANM, rINNM)* ⊗

Acetato de fluprednideno; Fluprednidène, Acétate de; Fluprednideni Acetas; Fluprednideno, acetato de; Fluprednylidene 21-Acetate; Флупреднидена ацетат.

9α-Fluoro-11β,17α,21-trihydroxy-16-methylenepregna-1,4-diene-3,20-dione 21-acetate.

$C_{24}H_{29}FO_6$=432.5

CAS — 2193-87-5 (fluprednidene); 1255-35-2 (fluprednidene acetate).

ATC — D07AB07.

ATC Vet — QD07AB07.

UNII — GE65DV564S.

Profile

Fluprednidene acetate is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.1% cream, or as an ointment containing 0.05% or 0.1%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluprednidene as

not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Decoderm; *Belg.*: Decoderm; *Ger.*: Decoderm; *Indon.*: Decoderm.

Multi-ingredient Preparations. *Austria*: Decoderm Compositum; Decoderm trivalent†; Vobaderm; *Belg.*: Decoderm Compositum†; *Ger.*: Candio-Hermal Plus; Crinohermal fem; Decoderm Comp; Decoderm tri; Sali-Decoderm; Vobaderm; *Gr.*: Antimycotic; Catrigel; Combi; Conazol; Decoderm Trivalente-N; Domycotin; Edmudo; Expectein; Feminella; Finicort; Flenazole; Flumicomplex; Fluniprol; Flunovon; Fosemyk; Fumicon; Ilferit; Micoflup; Micogen; Miflert†; Milfer; Oxigon; Panderm; Panmyk; Sarmel; Verdal; *Indon.*: Decoderm 3; Gentacortin†; *Ital.*: Decoder Micoflu; *Switz.*: Decoderm bivalent; *UK*: Acorvio Plus.

Fluticasone *(BAN, rINN)* ⊗

Fluticasona; Fluticasonum; Флутиказон.

S-(Fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate.

$C_{22}H_{27}F_3O_4S$=444.5

CAS — 90566-53-3.

ATC — D07AC17; R01AD08; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR03BA05.

UNII — CUT2W21N7U.

Fluticasone Furoate *(BANM, USAN, rINN)* ⊗

Fluticasonum Furoas; Furoate de Fluticasone; Furoato de fluticasona; GW-685698X; Флутиказон Фуроат.

6α,9-Difluoro-17-[[(fluoromethyl)sulfanyl]carbonyl]-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate.

$C_{27}H_{29}F_3O_6S$=538.6

CAS — 397864-44-7.

ATC — D07AC17; R01AD08; R01AD12; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR01AD12; QR03BA05.

UNII — JS86977WNV.

Fluticasone Propionate *(BANM, USAN, rINNM)* ⊗

CCI-18781; Fluticasona, propionato de; Fluticasone, propionate de; Fluticasoni Propionas; Fluticasonpropionat; Flutikasonipropionaatti; Flutikasonpropionat; Flutikason-propionát; Flutikazon Propiyonat; Flutikazono propionatas; Propionato de fluticasona; Флутиказона Пропионат.

S-Fluoromethyl 6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate 17-propionate.

$C_{25}H_{31}F_3O_5S$=500.6

CAS — 80474-14-2.

ATC — D07AC17; R01AD08; R03BA05.

ATC Vet — QD07AC17; QR01AD08; QR03BA05.

UNII — O2GMZ0LF5W.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Fluticasone Propionate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Fluticasone Propionate). Micronised fluticasone propionate is a fine white powder. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

Uses and Administration

Fluticasone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is given as the propionate or furoate ester; the latter is reported to have enhanced affinity for the glucocorticoid receptor. Fluticasone is stated to exert a topical effect on the lungs without significant systemic effects at usual doses, due to its low systemic bioavailability (but see Adrenal Suppression, p. 1639.1).

Fluticasone propionate is used by powder or aerosol inhalation for the prophylaxis of **asthma** (below). Typical initial doses in the UK range from 100 micrograms twice daily in mild asthma up to 500 micrograms twice daily in severe asthma, adjusted according to response; some patients may benefit from doses up to 1 mg twice daily under specialist supervision. The drug may also be given via a nebuliser in severe chronic asthma. Usual doses are 0.5 to 2 mg twice daily. In the USA, doses by powder inhalation are similar to those in the UK. The aerosol inhalation formulations contain 50, 125, or 250 micrograms of fluticasone propionate in each metered spray, which delivers 44, 110, or 220 micrograms, respectively from the actuator. Doses are therefore expressed in these units; dosage ranges from 88 micrograms twice daily to 880 micrograms twice daily, depending on previous therapy.

Fluticasone furoate is also given by dry powder inhalation in asthma prophylaxis; it is available in combination inhalers that also contain vilanterol trifenatate (p. 1239.3). The dose of fluticasone furoate may be expressed as the amount in each available dose (100 micrograms) or as the delivered dose leaving the mouthpiece (92 micrograms). A delivered dose of 92 micrograms is inhaled once daily; this may be increased to 184 micrograms once daily if necessary.

Fluticasone is used, usually with a long-acting beta$_2$ agonist, for the treatment of **chronic obstructive pulmonary disease** (below). Fluticasone propionate is given as a powder or aerosol inhalation in doses of 500 micrograms twice daily. Fluticasone furoate is given by dry powder inhalation in a delivered dose of 92 micrograms once daily.

Fluticasone is administered by nasal spray in the prophylaxis and treatment of **allergic rhinitis** (p. 1639.1). The usual dose of fluticasone propionate is 100 micrograms into each nostril once daily, increased if necessary to 100 micrograms into each nostril twice daily. A maintenance dose of 50 micrograms in each nostril once daily may be effective. Fluticasone furoate is also used in the management of allergic rhinitis, and is given in a starting dose of 55 micrograms into each nostril once daily. When the maximum benefit has been achieved and symptoms controlled, the dose should be reduced to the minimum effective dose; 27.5 micrograms into each nostril once daily may be sufficient to maintain control of symptoms.

Fluticasone propionate drops are used in the treatment of **nasal polyps**, 200 micrograms should be instilled into each nostril once or twice daily for at least 4 to 6 weeks.

Fluticasone propionate is applied topically in the treatment of various **skin disorders**. Creams and ointments containing 0.05% and 0.005%, respectively are available. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

For doses used in children, see below.

Administration in children. Fluticasone propionate is used by powder or aerosol inhalation for the prophylaxis of **asthma** in children. The typical initial dose in the UK for children aged 4 to 16 years old is 50 to 100 micrograms twice daily, increased to 200 micrograms twice daily if necessary. The drug may also be given via a nebuliser in the management of acute exacerbations of asthma in children; those aged 4 to 16 years may be given 1 mg twice daily. In the USA, doses by powder inhalation are similar to those in the UK, at 50 to 100 micrograms twice daily in children aged from 4 to 11 years old. The aerosol inhalation formulation licensed for use in children contains 50 micrograms of fluticasone propionate in each metered spray, which delivers 44 micrograms from the actuator. Doses are therefore expressed in multiples of this amount and children aged 4 to 11 years are given 88 micrograms twice daily.

Fluticasone is administered by nasal spray in the prophylaxis and treatment of **allergic rhinitis**. For children aged 4 to 11 years old, the usual dose of fluticasone propionate is 50 micrograms into each nostril once daily, increased if necessary to 50 micrograms into each nostril twice daily. Fluticasone furoate is also used in the management of allergic rhinitis. Children aged 2 to 11 years may be started on 27.5 micrograms into each nostril once daily, which may be increased to 55 micrograms into each nostril once daily if necessary to control symptoms. The dose may then be reduced to 27.5 micrograms into each nostril once daily to maintain control.

Older children and adolescents may be given adult doses for asthma and rhinitis (see above).

In the treatment of **nasal polyps**, fluticasone propionate may be given to children aged 16 years and older using adult doses (see above).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Some references to the use of fluticasone propionate for asthma are given below,[1-14] including one to a study indicating that increasing the dose of inhaled fluticasone did not produce increased benefit.[1]

1. Boe J, *et al.* High-dose inhaled steroids in asthmatics: moderate efficacy gain and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. *Eur Respir J* 1994; 7: 2179–84.
2. Jarvis B, Faulds D. Inhaled fluticasone propionate: a review of its therapeutic efficacy at dosages ≤ 500 micrograms/day in adults and adolescents with mild to moderate asthma. *Drugs* 1999; 57: 769–803.
3. Bisgaard H, *et al.* The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: a dose comparison study. *Am J Respir Crit Care Med* 1999; 160: 126–31.
4. ZuWallack R, *et al.* Long-term efficacy and safety of fluticasone propionate powder administered once or twice daily via inhaler to patients with moderate asthma. *Chest* 2000; 118: 303–312.
5. Holt S, *et al.* Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001; 323: 253–6.
6. Purucker MB, *et al.* Inhaled fluticasone propionate by diskus in the treatment of asthma: a comparison of the efficacy of the same nominal dose given either once or twice a day. *Chest* 2003; 124: 1584–93.
7. Masoli M, *et al.* Clinical dose-response relationship of fluticasone propionate in adults with asthma. *Thorax* 2004; 59: 16–20.
8. Masoli M, *et al.* Systematic review of the dose-response relation of inhaled fluticasone propionate. *Arch Dis Child* 2004; 89: 902–7.
9. Lasserson TJ, *et al.* Fluticasone versus 'extrafine' HFA-beclomethasone dipropionate for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 11/03/10).
10. Guilbert TW, *et al.* Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; 354: 1985–97.
11. Adams N, *et al.* Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 22/08/08).
12. Adams NP, *et al.* Fluticasone versus placebo for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 11/03/10).
13. Adams NP, *et al.* Fluticasone at different doses for chronic asthma in adults and children. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2008 (accessed 11/03/10).
14. McKeage K, Keam SJ. Salmeterol/fluticasone propionate: a review of its use in asthma. *Drugs* 2009; 69: 1799–1828.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

References and reviews.

1. Fenton C, Keating GM. Inhaled salmeterol/fluticasone propionate: a review of its use in chronic obstructive pulmonary disease. *Drugs* 2004; 64: 1975–96.
2. Keating GM, McCormack PL. Salmeterol/fluticasone propionate: a review of its use in the treatment of chronic obstructive pulmonary disease. *Drugs* 2007; 67: 2383–2405.
3. Martinez FJ, *et al.* Fluticasone furoate/vilanterol (100/25; 200/25 micrograms) improves lung function in COPD: a randomised trial. *Respir Med* 2013; 107: 550–9.

Cough. A small study in children with persistent nocturnal cough compared fluticasone propionate 1 mg twice daily for 3 nights, followed by 500 micrograms twice daily for 11 nights, given by metered-dose inhaler, with placebo. Coughs reduced significantly by nights 15 and 16 in the children given the corticosteroid. However, both groups improved significantly compared to baseline, leading the authors to conclude that inhaled corticosteroids should not be given at the time of presentation of persistent nocturnal cough. If they are given, then a 2-week course of high dose corticosteroids may benefit some children.[1] In a controlled crossover study in adult patients with chronic cough, inhaled fluticasone 500 micrograms twice daily for 14 days significantly improved certain measurements of cough, although overall reduction in cough severity was modest.[2] In adults with a cough lasting more than 2 weeks, fluticasone 500 micrograms twice daily for 2 weeks decreased cough scores from day 5 onwards in non-smokers.[3]

1. Davies MJ, *et al.* Persistent nocturnal cough: randomised controlled trial of high dose inhaled corticosteroid. *Arch Dis Child* 1999; 81: 38–44.
2. Chaudhuri R, *et al.* Effect of inhaled corticosteroids on symptom severity and sputum mediator levels in chronic persistent cough. *J Allergy Clin Immunol* 2004; 113: 1063–70.
3. Ponsioen BP, *et al.* Efficacy of fluticasone on cough: a randomised controlled trial. *Eur Respir J* 2005; 25: 147–52.

Eczema. In a study in patients with moderate to severe eczema (p. 1684.1), fluticasone propionate 0.05% cream or 0.005% ointment was applied once or twice daily for 4 weeks; if eczema stabilised, either the cream, the ointment, or an emollient placebo was then applied on 2 days per week, for up to 16 weeks. Fluticasone cream reduced the risk of relapse to about one-sixth of that of placebo, whereas the ointment formulation reduced the risk to about half; median times to relapse were similar for both fluticasone formulations. The formulations were originally expected to be of similar potency.[1] Others have commented[2] that caution should be exercised in generalising these results to primary care settings where most cases of eczema are likely to be mild, and relapses infrequent.

1. Berth-Jones J, *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; 326: 1367.
2. Williams HC. Twice-weekly topical corticosteroid therapy may reduce atopic dermatitis relapses. *Arch Dermatol* 2004; 140: 1151–2.

Inflammatory bowel disease. Fluticasone propionate, given orally, has produced variable results in the treatment of Crohn's disease[1] and ulcerative colitis;[2,3] some benefit was also reported in coeliac disease.[4] The dose was 5 mg four times daily but some consider[2] higher doses necessary.

For a review of the management of inflammatory bowel disease, including the role of corticosteroids, see p. 1808.3.

1. Carpani de Kaski M, *et al.* Fluticasone propionate in Crohn's disease. *Gut* 1991; 32: 657–61.
2. Hawthorne AB, *et al.* Double blind trial of oral fluticasone propionate v prednisolone in the treatment of active ulcerative colitis. *Gut* 1993; 34: 125–8.
3. Angus P, *et al.* Oral fluticasone propionate in active distal ulcerative colitis. *Gut* 1992; 33: 711–14.
4. Mitchison HC, *et al.* A pilot study of fluticasone propionate in untreated coeliac disease. *Gut* 1991; 32: 260–5.

Nasal polyps. For discussion of the value of corticosteroids in the treatment of nasal polyps, including reference to the use of fluticasone, see p. 1608.2.

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1. Some further references to the use of fluticasone in rhinitis are given below.

1. Wiseman LR, Benfield P. Intranasal fluticasone propionate: a reappraisal of its pharmacology and clinical efficacy in the treatment of rhinitis. *Drugs* 1997; 53: 885–907.
2. McCormack PL, Scott LJ. Fluticasone furoate: intranasal use in allergic rhinitis. *Drugs* 2007; 67: 1905–15.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). Hypersensitivity reactions have occurred with fluticasone. Eosinophilic conditions, including Churg-Strauss syndrome, have been reported rarely, in most cases after a transfer from oral corticosteroid therapy.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Inhalation or nasal use of large amounts of fluticasone may produce systemic effects also (see below).

Adrenal suppression. Despite the fact that inhaled fluticasone is generally thought to lack systemic effects at therapeutic doses, a study in 25 healthy subjects[1] indicated that fluticasone propionate as single inhaled doses of 250, 500, and 1000 micrograms did produce a reduction in plasma cortisol, indicating suppression of the hypothalamic-pituitary-adrenal axis to some degree. Others have also found evidence of adrenal suppression with fluticasone,[2-5] particularly at high doses and in children,[6] and the effect may be more marked with repeated than with single doses.[4,6-8] Several cases of adrenal crisis have been associated with high-dose inhaled fluticasone,[9,10] including at least one fatality.[6] It has been recommended that children using inhaled fluticasone at doses above 400 micrograms daily should have adrenal function monitoring and a written plan for emergency corticosteroid replacement therapy.[6]

1. Grahnén A, *et al.* An assessment of the systemic activity of single doses of inhaled fluticasone propionate in healthy volunteers. *Br J Clin Pharmacol* 1994; 38: 521–5.
2. Clark DJ, *et al.* Comparative systemic bioactivity of inhaled budesonide and fluticasone propionate in asthmatic children. *Br J Clin Pharmacol* 1996; 42: 264P.
3. Rohatagi S, *et al.* Dynamic modeling of cortisol reduction after inhaled administration of fluticasone propionate. *J Clin Pharmacol* 1996; 36: 938–41.
4. Clark DJ, Lipworth BJ. Adrenal suppression with chronic dosing of fluticasone propionate compared with budesonide in adult asthmatic patients. *Thorax* 1997; 52: 55–8.
5. Eid N, *et al.* Decreased morning serum cortisol levels in children with asthma treated with inhaled fluticasone propionate. *Pediatrics* 2002; 109: 217–21.
6. Paton J, *et al.* Adrenal responses to low dose synthetic ACTH (Synacthen) in children receiving high dose inhaled fluticasone. *Arch Dis Child* 2006; 91: 808–13.
7. Lönnebo A, *et al.* An assessment of the systemic effects of single and repeated doses of inhaled fluticasone propionate and inhaled budesonide in healthy volunteers. *Eur J Clin Pharmacol* 1996; 49: 459–63.
8. Wilson AM, *et al.* Adrenal suppression with high doses of inhaled fluticasone propionate and triamcinolone acetonide in healthy volunteers. *Eur J Clin Pharmacol* 1997; 53: 33–7.
9. Todd GRG, *et al.* Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. *Arch Dis Child* 2002; 87: 457–61.
10. Adverse Drug Reactions Advisory Committee (ADRAC). Fluticasone and adrenal crisis. *Aust Adverse Drug React Bull* 2003; 22: 6. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0304.htm (accessed 06/05/04)

Aspergillosis. The fungal infection aspergillosis has been reported in patients receiving inhaled[1,2] and intranasal[3] fluticasone.

1. Fairfax AJ, *et al.* Laryngeal aspergillosis following high dose inhaled fluticasone therapy for asthma. *Thorax* 1999; 54: 860–1.
2. Leav BA, *et al.* Invasive pulmonary aspergillosis associated with high-dose inhaled fluticasone. *N Engl J Med* 2000; 343: 586.
3. Bratton RL, *et al.* Aspergillosis related to long-term nasal corticosteroid use. *Mayo Clin Proc* 2002; 77: 1353–7.

Effects on the bones. For studies of the effects on bone of inhaled fluticasone, compared with beclometasone, see p. 1622.2.

Effects on the muscles. Proximal myopathy has been reported in children receiving high-dose inhaled fluticasone;[1] the patients recovered after replacement of fluticasone with alternative corticosteroid therapy.

1. De Swert LF, *et al.* Myopathy in children receiving high-dose inhaled fluticasone. *N Engl J Med* 2004; 350: 1157–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies fluticasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Fluticasone propionate is poorly absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism; oral bioavailability is reported to be only about 1%.

References.

1. Mackie AE, *et al.* Pharmacokinetics of intravenous fluticasone propionate in healthy subjects. *Br J Clin Pharmacol* 1996; 41: 539–42.
2. van Boxtel CJ, Sheffer AL, eds. The pharmacokinetics of fluticasone propionate. *Clin Pharmacokinet* 2000; 39 (suppl): 1–54.
3. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol* 2001; 51: 103–5.
4. Allen A, *et al.* Absolute bioavailability of intranasal fluticasone furoate in healthy subjects. *Clin Ther* 2007; 29: 1415–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alenys; Balivent; Crivanil; Cutivate; Flixonase; Flixotide; Fluti-K; Fluticort; Inhalan; Lidil Cort; Lirtodac; Proair; Rinisona; *Austral.*: Avamys; Flixonase Allergy & Hayfever 24 Hour; Flixonase; Flixotide; *Austria*: Avamys; Cutivate; Flixonase; Flixotide; *Belg.*: Avamys; Cutivate; Flixonase; Flixotide; *Braz.*: Avamys; Flixonase; Flixotide; Flutican; Fluticaps; Flutivate; Plurair; *Canad.*: Avamys; Cutivate; Flonase; Flovent; *Chile*: Albeoler; Alenys; Avamys; Brexonase; Brexovent†; Flixonase; Flixotide; Flucomix; Flusona; Fluticort; Flutivate; Nebulex; Raffonin; *China*: Cutivate (克廷肤); Flixonase (辅舒良); Flixotide (辅舒丽); *Cz.*: Alergonase†; Alisade; Avamys; Cutivate; Flixonase†; Flixotide; Nasofan; *Denm.*: Avamys; Cutivat; Flixonase; Flixotide; Flutide; *Fin.*: Flixonase; Flixotide; Flutide; Nasofan; *Fr.*: Avamys; Flixonase; Flixotide; Flixovate; *Ger.*: Atemur†; Avamys; Flutica†; Flutide; Flutivate; *Gr.*: Alerxem; Avamys; Bocacort-S; Cortixide; Dermocort; Flicazen; Flihaler; Flixocort; Flixoderm; Flixonase; Flixotide; Flixotide; Flucortis; Flutarzole; Fluticapen; Flutikrem; Flutinasal; Flutizal; Nasofan; Salenga; Ybecor; *Hong Kong*: Avamys; Cutivate; Dalman; Dermcasone; Flixonase; Flixotide; Lutisone; Nasofan; *Hung.*: Avamys; Cutivate; Flixonase; Flixotide; Flutirin; *India*: Flixonase; Floease; Flohale; Flomist; Flucasia; Fluster; Flute; Fluticare; Fluticone; Flutiflo; Flutivate; Flutopic; Moliderm; Nezaflo; Otrivin-C; Zoflut; *Indon.*: Avamys; Cutivate†; Flixonase; Flixotide; Medicort; *Irl.*: Avamys; Flixonase; Flixotide; Nasofan; *Israel*: Allegro; Avamys; Flixonase; Flixotide; Flutitrim; *Ital.*: Avamys; Flixoderm; Flixonase; Flixotide; Fluspiral; Fluticrem; Nasofan; Ticavent; *Jpn*: Flonase†; *Malaysia*: Avamys; Cutivate; Flixonase; Flixotide; Flomist; *Mex.*: Avamys; Canetif†; Cutivate; Flixonase; Flixotide; *Neth.*: Avamys; Cortifil; Cutivate; Flixonase; Flixotide; Fluticrem; Flutide; *Norw.*: Avamys; Flutide; Flutivate; *NZ*: Flixonase; Flixotide; Nasaclear†; *Philipp.*: Avamys; Cutivate; Flixotide; Nasoflo; *Pol.*: Alisade; Avamys; Cutivate; Fanipos; Flixonase; Flixotide; *Port.*: Asmatil; Asmo-Lavi; Avamys; Brisovent; Cutivate; Eustidil; Flixotaide; Flutaide; Rontilona; Ubizol; *Rus.*: Avamys (Авамис); Cutivate (Кутивейт); Flixonase (Фликсоназе); Flixotide (Фликсотид); Nazarel (Назарел); *S.Afr.*: Avamys; Cutivate; Flixonase; Flixotide; Flohale DP; Flomist; Flonase; *Singapore*: Avamys; Cutivate; Flixonase; Flixotide; Flutitrim; *Spain*: Avamys; Cutivate; Flixonase; Flixotide; Fluinol; Flunutrac; Flusonal; Fluticrem; Inalacor; Nasofan†; Rinosone; Trialona; *Swed.*: Avamys; Flutide; Flutivate; *Switz.*: Avamys; Axotide; Cutivate; Flutinase; Nasofan; *Thai.*: Avamys; Flixonase; Flixotide; *Turk.*: Avamys; Brethal; Cutivate; Dalman; Flixonase; Flixotide; *UAE*: Potencort; *UK*: Avamys; Cutivate; Flixotide; Nasofan; Pirinase; *Ukr.*: Avamis (Авамис); Cutivate (Кутивейт); Flixonase (Фликсоназе); Flixotide (Фликсотид); Nasofan (Назофан); *USA*: Cutivate; Flonase; Flovent; Veramyst; *Venez.*: Cutivate; Flixonase; Flixotide; Fluticort.

Multi-ingredient Preparations. *Arg.*: Crivanil Plus; Flutivent; Lirtodac Plus; Neumotide; Proair Bronquial; Seretide; *Austral.*: Seretide; *Austria*: Seretide; Viani; *Belg.*: Flutiform; Seretide; Viani†; *Braz.*: Seretide; *Canad.*: Advair; *Chile*: Aerometrol Plus; Aurituss; Brexotide; Flunacross-S; Fluxamol; Seretide; *China*: Seretide (舒利迭); *Cz.*: Duaspir†; Seretide; *Denm.*: Aliflus†; Seretaide; Seretide; *Fin.*: Dymista; Flutiform; Seretide; Viani; *Fr.*: Seretide; *Ger.*: Atmadisc; Viani; *Gr.*: Byany; Rolenium; Seretide; Viani; *Hong Kong*: Seretide; *Hung.*: Seretide; Thoreus; *India*: Avessa; Azeflo; Combihale-FF; Combitide; Duonase; Esiflo; Flutibact; Flutticare-C; Fluticare-N; Forair; Nezalast; Seretide; Seroflo; *Indon.*: Seretide; *Irl.*: Seretide; Viani; *Israel*: Seretide; *Ital.*: Aliflus; Seretide; *Malaysia*: Seretide; *Mex.*: Flixovent; Seretide; *Neth.*: Aliflus; Brisair†; Flutiform; Iffeza; Seretide; *Norw.*: Flutiform; Seretide; *NZ*: Seretide; *Philipp.*: Salmeflo; Seretide; *Pol.*: Seretide; *Port.*: Brisomax; Maizar; Seretaide; Veraspir; *Rus.*: Seretide (Серетид); Tevacomb (Тевакомб); *S.Afr.*: Foxair; Sereflo; Seretide; *Singapore*: Seretide; *Spain*: Anasma; Brisair; Inaladuo; Plusvent; Seretide; *Swed.*: Seretide; *Switz.*: Seretide; *Thai.*: Seretide; Seroflo; *Turk.*: Respiro; Seretide; *UK*: Dymista; flutiform; Relvar Ellipta; Seretide; *Ukr.*: Seretide (Серетид); *USA*: Advair; Breo Ellipta; Dymista; *Venez.*: Seretide.

Pharmacopoeial Preparations

BP 2014: Fluticasone Cream; Fluticasone Inhalation Powder, pre-dispensed; Fluticasone Inhalation Powder; Fluticasone Nasal Drops; Fluticasone Nasal Spray; Fluticasone Ointment; Fluticasone Pressurised Inhalation;

USP 36: Fluticasone Propionate Cream; Fluticasone Propionate Inhalation Aerosol; Fluticasone Propionate Inhalation Powder; Fluticasone Propionate Nasal Spray; Fluticasone Propionate Ointment.

Halcinonide *(BAN, USAN, rINN)* ⊗

Alcinonide; Halcinonid; Halcinónida; Halcinonidum; Halsinonid; Halsinonidi; SQ-18566; Гальцинонид.

21-Chloro-9α-fluoro-11β-hydroxy-16α,17α-isopropylidenedioxypregn-4-ene-3,20-dione.

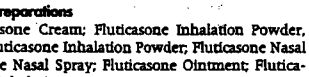
$C_{24}H_{32}ClFO_5$=455.0

CAS — 3093-35-4.

ATC — D07AD02.

ATC Vet — QD07AD02.

UNII — SI86V6QNEG.



Pharmacopoeias. In *Chin.* and *US.*

USP 36: (Halcinonide). A white to off-white, odourless, crystalline powder. Insoluble in water and in hexanes; slightly soluble in alcohol and in ether; soluble in acetone and in chloroform.

Profile

Halcinonide is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a 0.1% cream, lotion, or ointment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Halog; *Canad.*: Halog†; *China*: Ha Le Te (哈乐特); *Cz.*: Betacorton†; *Gr.*: Ascochrom; Hamiltoderm-D; *Hong Kong*: Halog†; *India*: Cortilate; *Indon.*: Halog†; *Ital.*: Halciderm; *Mex.*: Dermalog; *Switz.*: Betacortone; *Turk.*: Volog; *USA*: Halog; *Venez.*: Halog.

Multi-ingredient Preparations. *Braz.*: Halog Capilar; *Cz.*: Betacorton S†; Betacorton U†; *India*: Cobederm-H†; Cortilate-N; Cortilate-S; Halog-E; Orkid-S; *Ital.*: Halciderm Combi; Halciderm; *Mex.*: Dermalog-C; *Switz.*: Betacortone S; Betacortone; *Turk.*: Betacorton; *Venez.*: Halcicomb; Halog.

Pharmacopoeial Preparations

USP 36: Halcinonide Cream; Halcinonide Ointment; Halcinonide Topical Solution.

Halometasone *(rINN)* ⊗

C-48401-Ba; Halometason; Halometasona; Halométasone; Halometasoni; Halometasonum; Halometazon; Halometha-sone; Галометазон.

2-Chloro-6α,9-difluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.

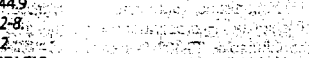
$C_{22}H_{27}ClF_2O_5$=444.9

CAS — 50629-82-8.

ATC — D07AC12.

ATC Vet — QD07AC12.

UNII — J69Z9UU41Z.



Profile

Halometasone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream containing 0.05% of halometasone monohydrate.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Aoneng (澳能); Sicorten (适确得); Sicorten Plus (新适确得); *Hong Kong*: Sicorten; *Spain*: Sicorten†; *Switz.*: Sicorten†; *Turk.*: Sicorten.

Multi-ingredient Preparations. *Ger.*: InfectoCortiSept; Sicorten Plus†; *Spain*: Sicorten Plus†; *Switz.*: Sicorten Plus.

Hydrocortisone *(BAN, rINN)* ⊗

Anti-inflammatory Hormone; Compound F; Cortisol; Hidrocortisona; Hidrokortizon; Hidrokortizonas; Hydrocortison; Hydrocortisonum; Hydrokortison; Hydrokortisoni; Hydrokortyzon; 17-Hydroxycorticosterone; NSC-10483; Гидрокортизон.

11β,17α,21-Trihydroxypregn-4-ene-3,20-dione.

$C_{21}H_{30}O_5$=362.5

CAS — 50-23-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QD07XA01; QH02AB09; QS01BA02; QS01CB03; QS02BA01.

UNII — WI4X0X7BPJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Hydrocortisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol and in acetone; slightly soluble in dichloromethane. Protect from light.

USP 36: (Hydrocortisone). A white to practically white, odourless, crystalline powder. Very slightly soluble in water and in ether; soluble 1 in 40 of alcohol and 1 in 80 of acetone; slightly soluble in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Hydrocortisone Acetate *(BANM, rINNM)* ⊗

Acetato de hidrocortisona; Cortisol Acetate; Hidrocortisona, acetato de; Hidrokortizon Asetat; Hidrokortizon-acetát; Hidrokortizono acetatas; Hydrocortisonacetat; Hydrocortisone, Acétate d'; Hydrocortisoni Acetas; Hydrokortisonacetat; Hydrokortison-acetát; Hydrokortisoniasetaatti; Hydrokortyzonu octan; Гидрокортизона Ацетат.

Hydrocortisone 21-acetate.

$C_{23}H_{32}O_6$=404.5

CAS — 50-03-3.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 3X7931PO74.

NOTE. HCOR is a code approved by the BP 2014 for use on single unit doses of eye drops containing hydrocortisone acetate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrocortisone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in dichloromethane. Protect from light.

USP 36: (Hydrocortisone Acetate). A white to practically white, odourless, crystalline powder. Insoluble in water; soluble 1 in 230 of alcohol and 1 in 200 of chloroform.

Hydrocortisone Buteprate *(BANM, rINNM)* ⊗

Buteprato de hidrocortisona; Hidrocortisona, buteprato de; Hydrocortisone, Butéprate d'; Hydrocortisone Butyrate Propionate; Hydrocortisone Probutate (USAN); Hydrocortisoni Butepras; TS-408; Гидрокортизона бутепрат.

Hydrocortisone 17-butyrate 21-propionate.

$C_{28}H_{40}O_7$=488.6

CAS — 72590-77-3.

ATC — D07AB11.

ATC Vet — QD07AB11.

UNII — O6550D6K3A.

Hydrocortisone Butyrate *(BANM, USAN, rINNM)* ⊗

Butirato de hidrocortisona; Cortisol Butyrate; Hidrocortisona, butirato de; Hidrokortizon Bütirat; Hydrocortisone, Butyrate d'; Hydrocortisoni Butiras; Гидрокортизона бутират.

Hydrocortisone 17α-butyrate.

$C_{25}H_{36}O_6$=432.6

CAS — 13609-67-1.

ATC — D07AB02.

ATC Vet — QD07AB02.

UNII — 05RMF7YPWN.

Pharmacopoeias. In *Chin.*, *Jpn*, and *US*.

USP 36: (Hydrocortisone Butyrate). A white to practically white, practically odourless crystalline powder. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; freely soluble in chloroform; slightly soluble in ether.

Hydrocortisone Cipionate *(BANM, rINNM)* ⊗

Cipionato de hidrocortisona; Cortisol Cypionate; Hidrocortisona, cipionato de; Hydrocortisone, Cipionate d'; Hydrocortisone Cyclopentylpropionate; Hydrocortisone Cypionate; Hydrocortisoni Cipionas; Гидрокортизона Ципионат.

Hydrocortisone 21-(3-cyclopentylpropionate).

$C_{29}H_{42}O_6$=486.6

CAS — 508-99-6.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 4XDY25L70B.

Hydrocortisone Hydrogen Succinate *(BANM, rINNM)* ⊗

Cortisol Hemisuccinate; Hidrocortisona, hidrogenosuccinato de; Hidrogenosuccinato de hidrocortisona; Hidrokortizon-hidrogén-szukcinát; Hidrokortizono hemisukcinatas; Hydrocortisone Hemisuccinate; Hydrocortisone, Hémisuccinate d'; Hydrocortisone, hydrogénosuccinate d'; Hydrocortisone Succinate; Hydrocortisonhydrogensuccinat; Hydrocortisoni Hemisuccinas; Hydrocortisoni hydrogenosuccinas; Hydrokortison-hydrogen-sukcinát; Hydrokortisonivetysuksinaatti; Hydrokortisonvätesuccinat; Гидрокортизона Гемисукцинат.

Hydrocortisone 21-(hydrogen succinate).

$C_{25}H_{34}O_8$=462.5

CAS — 2203-97-6 (anhydrous hydrocortisone hydrogen succinate); 83784-20-7 (hydrocortisone hydrogen succinate monohydrate).

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — LJU00Z1Z84.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*. *US* allows the anhydrous form or the monohydrate.

Ph. Eur. 8: (Hydrocortisone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; freely soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali carbonates and alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Hydrocortisone Hemisuccinate). It contains one molecule of water of hydration or is anhydrous. Store in airtight containers.

Hydrocortisone Sodium Phosphate *(BANM, rINNM)* ⊗

Cortisol Sodium Phosphate; Fosfato sódico de hidrocortisona; Hidrocortisona, fosfato sódico de; Hydrocortisone, Phosphate Sodique d'; Natrii Hydrocortisoni Phosphas; Натрия Гидрокортизона Фосфат.

Hydrocortisone 21-(disodium orthophosphate).

$C_{21}H_{29}Na_2O_8P$=486.4

CAS — 6000-74-4.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 0388G963HY.

Pharmacopoeias. In *Br.*, *Jpn*, and *US*.

BP 2014: (Hydrocortisone Sodium Phosphate). A white or almost white, hygroscopic powder. Freely soluble in water; practically insoluble in dehydrated alcohol and in chloroform. A 0.5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 36: (Hydrocortisone Sodium Phosphate). A white to light yellow, odourless or practically odourless, exceedingly hygroscopic, powder. Soluble 1 in 1.5 of water; slightly soluble in alcohol; practically insoluble in chloroform, in dioxan, and in ether. Store in airtight containers.

Hydrocortisone Sodium Succinate *(BANM, rINNM)* ⊗

Cortisol Sodium Succinate; Hidrocortisona, succinato sódico de; Hydrocortisone, Succinate Sodique d'; Hydrocortisoni Natrii Succinas; Hydrokortyzonu bursztynianu sól sodowa; Succinato sódico de hidrocortisona; Гидрокортизона Натрия Сукцинат.

Hydrocortisone 21-(sodium succinate).

$C_{25}H_{33}NaO_8$=484.5

CAS — 125-04-2.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — S0LQB69S1Z.

Pharmacopoeias. In *Chin.*, *Int.*, *It.*, *Jpn.*, *Pol.*, and *US*.

USP 36: (Hydrocortisone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Very soluble in water and in alcohol; very slightly soluble in acetone; insoluble in chloroform. Store in airtight containers. Protect from light.

Hydrocortisone Valerate *(BANM, USAN, rINNM)* ⊗

Cortisol Valerate; Hidrocortisona, valerato de; Hydrocortisone, Valérate d'; Hydrocortisoni Valeras; Valerato de hidrocortisona; Гидрокортизона Валерат.

Hydrocortisone 17-valerate.

$C_{26}H_{38}O_6$=446.6

CAS — 57524-89-7.

ATC — A01AC03; A07EA02; C05AA01; D07AA02; H02AB09; S01BA02; S02BA01.

ATC Vet — QA01AC03; QA07EA02; QC05AA01; QD07AA02; QH02AB09; QS01BA02; QS02BA01.

UNII — 68717P8FUZ.

Pharmacopoeias. In *US*.

Uses and Administration

Hydrocortisone is a corticosteroid with both glucocorticoic and to a lesser extent mineralocorticoid activity (p. 1597.1) 20 mg of hydrocortisone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. As cortisol it is the most important of the mainly glucocorticoid corticosteroids secreted by the adrenal cortex. Hydrocortisone is used usually with a more potent mineralocorticoid, for replacement therapy in adrenocortical insufficiency (p. 1600.2). It may also be used for its glucocorticoic properties in other conditions for which corticosteroic therapy is indicated (p. 1597.3) but drugs with fewer mineralocorticoid effects tend to be preferred for the long-term systemic therapy of auto-immune and inflammatory disease.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of hydrocortisone:

- hydrocortisone acetate 112 mg
- hydrocortisone buteprate 135 mg
- hydrocortisone butyrate 119 mg
- hydrocortisone cipionate 134 mg
- hydrocortisone hydrogen succinate 128 mg
- hydrocortisone sodium phosphate 134 mg
- hydrocortisone sodium succinate 134 mg
- hydrocortisone valerate 123 mg

However, esterification generally alters potency and compounds with equivalent hydrocortisone content may not have equivalent clinical effect.

When given orally hydrocortisone free alcohol is usually used; the cipionate ester is used in some formulations. For *replacement therapy* in acute or chronic adrenocortical insufficiency the normal requirement is 20 to 30 mg daily (usually taken in 2 doses, the larger in the morning and the smaller in the early evening, to mimic the circadian rhythm of the body). Additional sodium chloride may be required if there is defective aldosterone secretion, but mineralocorticoid activity is usually supplemented by fludrocortisone acetate orally. Similar regimens have also been used to correct glucocorticoid deficiency in the salt-losing form of congenital adrenal hyperplasia (p. 1603.2).

Hydrocortisone may be given **intravenously**, by slow injection or infusion, in the form of a water-soluble derivative such as hydrocortisone sodium succinate or hydrocortisone sodium phosphate when a rapid effect is required in *emergencies*: such conditions are acute adrenocortical insufficiency caused by Addisonian or post-adrenalectomy crises, by the abrupt accidental withdrawal of therapy in corticosteroid-treated patients, or by the inability of the adrenal glands to cope with increased stress in such patients; certain allergic emergencies such as anaphylaxis; acute severe asthma (status asthmaticus—see

also p. 1195.2); and shock. The usual dose is the equivalent of 100 to 500 mg of hydrocortisone, repeated 3 or 4 times in 24 hours, according to the severity of the condition and the patient's response. Fluids and electrolytes should be given as necessary to correct any associated metabolic disorder. Similar doses to those specified above may also be given **intramuscularly** but the response is likely to be less rapid than that seen after intravenous doses. Corticosteroids are considered to be of secondary value in anaphylactic shock because of their relatively slow onset of action, but intravenous hydrocortisone may be a useful adjunct to adrenaline to prevent further deterioration in severely affected patients.

For doses used in children, see below.

In patients with adrenal deficiency states supplementary corticosteroid therapy may be necessary during some *surgical operations* and hydrocortisone sodium succinate or sodium phosphate may be given intramuscularly or intravenously before surgery. Various regimens have been proposed (see also Surgery, p. 1599.1). In patients taking more than 10 mg of oral prednisolone or its equivalent daily, the *BNF* recommends the following regimen:

- *minor surgery under general anaesthesia*, either the usual oral corticosteroid dose on the morning of surgery *or* hydrocortisone 25 to 50 mg (usually as the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is resumed after surgery
- *moderate or major surgery*, the usual oral corticosteroid dose on the morning of surgery, *plus* hydrocortisone 25 to 50 mg intravenously at induction, and followed by similar doses of hydrocortisone 3 times daily, for 24 hours after moderate surgery and 48 to 72 hours after major surgery; the usual corticosteroid dose is resumed once hydrocortisone injections are stopped

For **local injection** into soft tissues hydrocortisone is usually used in the form of the sodium phosphate or sodium succinate esters; doses in terms of hydrocortisone are usually 100 to 200 mg. For intra-articular injection hydrocortisone acetate is usually used in doses of 5 to 50 mg depending upon the size of the joint.

For **topical application** in the treatment of various skin disorders hydrocortisone and the acetate, buteprate, butyrate, and valerate esters are normally employed in creams, ointments, or lotions. Concentrations usually used have ranged from 0.1 to 2.5%. Although it is considered that hydrocortisone has fewer adverse effects on the skin and is less liable to cause adrenal suppression than the more potent topical corticosteroids (see p. 1599.2 for a rough guide to the clinical potencies of topical corticosteroids), it should be borne in mind that this property may be considerably modified both by the type of formulation or vehicle used and by the type of esterification present; other factors that may also influence the degree of absorption include the site of application, use of an occlusive dressing, the degree of skin damage, and the size of the area to which the preparation is applied.

Hydrocortisone or its esters are also available in a variety of other dosage forms including those for ophthalmic, aural, dental, and rectal application, for use in allergic and inflammatory disorders.

Other esters of hydrocortisone that have occasionally been used include the aceponate, caproate, glycyrrhetinate, and propionate. Esters such as the aceponate may show modified topical activity.

Administration in children. When given **orally** as *replacement therapy* in adrenocortical insufficiency, the *BNFC* suggests that neonates and children aged from 1 month to 18 years of age may be given hydrocortisone in usual doses of 8 to 10 mg/m² daily in 3 divided doses, although higher doses may be needed. Larger portions of the daily dose are given in the morning and smaller portions in the evening. In congenital adrenal hyperplasia, initial oral doses of 9 to 15 mg/m² daily in 3 divided doses may be used; again, higher doses may be needed and the dose should be adjusted according to response.

When used **intravenously** for *emergencies* such as acute adrenocortical insufficiency, the following doses may be given:

- neonates: initially 10 mg as a slow injection, then 100 mg/m² daily as a continuous infusion or in divided doses every 6 to 8 hours; the dose should be adjusted according to response and, when stable, reduced over 4 to 5 days to an oral maintenance dose
- 1 month to 12 years old: initially 2 to 4 mg/kg as a slow injection or infusion, then 2 to 4 mg/kg every 6 hours; the dose should be adjusted according to response and, when stable, reduced over 4 to 5 days to an oral maintenance dose
- 12 to 18 years old: 100 mg every 6 to 8 hours by slow injection or infusion

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Effects on fluid and electrolyte balance. A report of marked hypokalaemia and hypomagnesaemia associated with high-dose intravenous hydrocortisone therapy in an alcoholic patient with suspected immune thrombocytopenia.[1] Cardiac arrhythmias developed, and prolonged infusion of magnesium and potassium was required to restore normal plasma concentrations.

1. Ramsahoye BH, *et al.* The mineralocorticoid effects of high dose hydrocortisone. *BMJ* 1995; 310: 656–7.

Effects on the nervous system. For reports and comments on paraesthesia or perineal irritation associated with hydrocortisone sodium phosphate given intravenously, see p. 1617.3.

Hypersensitivity and anaphylaxis. References to hypersensitivity reactions and anaphylaxis associated with the intravenous use of hydrocortisone;[1-7] topical application can also result in hypersensitivity.[8]

1. Chan CS, *et al.* Hydrocortisone-induced anaphylaxis. *Med J Aust* 1984; 141: 444–6.
2. Seale JP. Anaphylactoid reaction to hydrocortisone. *Med J Aust* 1984; 141: 446.
3. Corallo CE, Sosnin M. Bronchospasm, tachycardia following intravenous hydrocortisone. *Aust J Hosp Pharm* 1985; 15: 103–4.
4. Al Mahdy H, Hall M. Anaphylaxis and hydrocortisone. *Ann Intern Med* 1988; 108: 487–8.
5. Fulcher DA, Katelaris CH. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate: a case report and literature review. *Med J Aust* 1991; 154: 210–14.
6. Kawane H. Anaphylactoid reaction to intravenous hydrocortisone sodium succinate. *Med J Aust* 1991; 154: 782.
7. Currie GP, *et al.* An unexpected response to intravenous hydrocortisone succinate in an asthmatic patient. *Br J Clin Pharmacol* 2005; 60: 342.
8. Wilkinson SM, *et al.* Hydrocortisone: an important cutaneous allergen. *Lancet* 1991; 337: 761–2.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrocortisone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief account of the pharmacokinetics of corticosteroids, see p. 1620.3.

Hydrocortisone is readily absorbed from the gastrointestinal tract and peak blood concentrations occur in about an hour. The plasma half-life is about 100 minutes. It is more than 90% bound to plasma proteins. Following intramuscular injection, the absorption of the water-soluble sodium phosphate and sodium succinate esters is rapid, while absorption of hydrocortisone free alcohol and its lipid-soluble esters is slower. Absorption of hydrocortisone acetate after intra-articular or soft-tissue injection is also slow. Hydrocortisone is absorbed through the skin, particularly in denuded areas.

Hydrocortisone is metabolised in the liver and most body tissues to hydrogenated and degraded forms such as tetrahydrocortisone and tetrahydrocortisol. These are excreted in the urine, mainly conjugated as glucuronides, with a very small proportion of unchanged hydrocortisone. Hydrocortisone readily crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Alfacort; Anusol-HC; Azuthidrona; Demacort; Fridalit; Hidrotisona; Lactid HC; Locoid; Medrocil; Microsona; Oralsone; Proavenal H; Schericurt†; Sirotamicin HC; Stiefcortil; Transderma H; ***Austral.***: Colifoam; Cortef; Cortic; Derm-Aid; DermAid; Egocort; Hycor; Hysone; Sigmacort; Siguent Hycor; Solu-Cortef; ***Austria***: Colifoam; Ekzemsalbe F; Hydoftal sine neomycino†; Hydrocortone; Hydroderm; Locoidon†; ***Belg.***: Azacortine; Cremicort-H; Locoid; Pannocort; Solu-Cortef; ***Braz.***: Androcortil; Ariscorten; Benzenil; Berlison; Cortisonal; Cortiston; Cortizol; Cortizon†; Hicortin†; Hidrocortex; Hidyn H; Locoid; Nutracort; Solu-Cortef; Stiefcortil; Therasona; Westcort†; ***Canad.***: Barriere-HC; Claritin Skin Itch Relief; Cortamed; Cortate; Cortef; Cortenema; Cortifoam; Cortoderm; Dermaflex HC; Emo-Cort; Hycort; Hyderm; Hydrosone; HydroVal; Neo-HC†; Novo-Hydrocort; Prevex HC; Sarna HC; Solu-Cortef; Soothing Cream; Westcort†; ***Chile***: Aquanil HC†; Calmurid; Cortisol; Efficort; Hipoge; Locoid; Nutracort; Pandel; Solu-Cortef; ***China***: Efficort (益芙可); Locoid (米可得); Youzhouer (尤卓尔); ***Cz.***: Locoid; ***Denm.***: Colifoam; Hyderm; Locoid; Mildison; Plenadren; Solu-Cortef; ***Fin.***: Ampikyy; Apocort; Bucort; Colifoam; Hyderm; Kyypakkaus; Locoid; Solu-Cortef; ***Fr.***: Aphilan; Calmicort; Colofoam; Cortapaisyl; Cortisedermyl; Dermaspraid Demangeaison†; Dermofenac Efficort; Hydracort†; Locoid; Mitocortyl†; ***Ger.***: Alfason; Colifoam; Ebenol; Fenistil Hydrocort†; Ficortril; Hydrocutan mild†; Hydrocutan; Hydrogalen; Hydroson; Laticort; Linola Akut; Linolacort Hydro; Muni; Munitren†; Neuroderm Akut; Pandel†; Posterisan cort; Retef†; Sanatison Mono†; Soventol HydroCort; Soventol HydroSpray; Systral Hydrocort†; ***Gr.***: Colifoam; Filocot; Lyo-Cortin; Nutracort; Rolak; Solu-Cortef; ***Hong Kong***: BF-Hycort†; Cortef; Cortosone†; Derm-Aid; Dhacort; Egocort; Hydrosone; Hytisone; Sigmacort; Solu-Cortef; Uni-Cort†; ***Hung.***: Cortef; Laticort; Locoid; Solu-Cortef; ***India***: Arvisone; Cardol; Cipcorlin; Cort-H; Cort-S; Cortygard; Cutisoft; Efcorlin; Eldercoid; Entofoam; Geocort; H-Cort; Hisone; Hobutide; HS; Hy-Sone; Hycort; Hycoson; Hyss; Hyver; Intacorlin; Irays; Labocort; Lacticare-HC; Locoid; Lycor; Lycortin-S; M-Cort; Multicort; Niscort; Novacort; Wycort; ***Indon.***: Berlicort; Calacort†; Enkacort; Lexacorton; Locoid†; Steroderm†; ***Irl.***: Colifoam; Corlan; Cortopin; Dioderm; Emucream HC†; Hc45; Hydrocortisyl; Hydrocortone; Locoid; Plenadren; Solu-Cortef; ***Israel***: Cortifoam; Cortizone; Efficort†; Lanacort; Solu-Cortef; ***Ital.***: Colifoam; Cortidro; Cortop; Dermirit; Dermocortal; Flebocortid; Foille Insetti; Idracemi; Lanacort; Lenirit; Locoidon; Sintotrat; Solu-Cortef; ***Jpn***: Pandel; Saxizon; ***Malaysia***: Derm-Aid; Efficort; Egocort; H-Cort; Hycort; Hydrocort; Solu-Cortef; ***Mex.***: Aquanil HC; Coillocort†; Efficort; Fadol†; Flebocortid; Flemex; Icorsan; Lacticare-HC; Locoid; Microsona; Nositrol; Nutracort; Solhidrol; Westcort; ***Neth.***: Buccalsone†; Cremicort; Locoid; Mildison†; Plenadren; Solu-Cortef; Zure oordruppels met hydrocortison; ***Norw.***: Colifoam†; Locoid; Mildison; Plenadren; Solu-Cortef; ***NZ***: BK HC; Colifoam; Derm-Aid; DP Hydrocortisone†; Egocort; Lemnis Fatty Cream HC; Lipocort; Locoid; Mildison; Skincalm; Solu-Cortef; ***Philipp.***: Biocort; Clovisone; Cortin; Cortizan; Costeron-H; Droxiderm; Efficort; Hovicor; Hycort; Hycortil; Hydrotopic; Lacticare-HC; Ocecor; Pharmacort; Primacort; Solu-Cortef; Sorvilor; Stericort; Syntesor; ***Pol.***: Corhydron; Hydrocort; Laticort; Locoid; Procortin; ***Port.***: Colifoam; Hidalone; Hydrocortone; Lactisona; Locoid; Pandel; Pandermil; Rapicort; Solu-Cortef; ***Rus.***: Cortef (Кортеф); Laticort (Латикорт); Locoid (Локоид); Sopolcort N (Сополькорт Н)†; ***S.Afr.***: Biocort; Covocort; Dilucort; Locoid; Mezzoderm; Mylocort; Procutan; Skincalm; Solu-Cortef; Stopitch; ***Singapore***: Cortisone; Derm-Aid; Dhacort; Efficort; Egocort; H-Cort; Hydrocort; Hydroderm; Nu-Derm Tolereen†; Solu-Cortef; ***Spain***: Actocortina; Aftasone; Calmiox; Ceneo; Dermosa Hidrocortisona; Hemodren; Hemorrane; Hidroaltesona; Hidrocisdin; Isdinium; Lactisona; Nutrasona; Oralsone; Scalpicin Capilar†; Schericur; Suniderma; ***Swed.***: Colifoam; Ficortril; Hyderm; Locoid; Mildison; Solu-Cortef; Uniderm†; ***Switz.***: Alfacortone; Hydrocortone; Locoid; Sanadermil; Solu-Cortef; ***Thal.***: H-Cort; HC; Hytisone; Lacticare-HC; Prevex HC†; Solu-Cortef; ***Turk.***: Cortimycine; Hipokort; Locoid; ***UAE***: Alfacort; ***UK***: Colifoam; Corlan†; Cortopin; Cortropin; Dermacort; Dioderm; Efcortelan†; Efcortesol; Exe-Cort; Hc45; Hydrocortistab; Hydrocortone†; Lanacort; Locoid; Mildison; Plenadren; Solu-Cortef; Zenoxone; ***Ukr.***: Laticort (Латикорт); Locoid (Локоид); Solu-Cortef (Солу-Кортеф); ***USA***: A-Hydrocort; Acticort; Ala-Cort; Anucort-HC; Aquanil HC; Aveeno Active Naturals Hydrocortisone; Bactine; CaldeCort; Carmol HC; Cetacort; Colocort; Cort-Dome; Cortaid; Cortef Feminine Itch; Cortef; Corticaine†; Corticool; Cortifoam; Cortizone; Dermarest Dri-Cort; Dermol HC; Dermolate; EarSol-HC; Gynecort; Hemril-HC; Hi-Cor; Hydrocortone; HydroSkin; Hytone; Itch-X; Lacticare-HC†; Lanacort; Locoid; Massengill Medicated; Neutrogena T/Scalp; Noble Formula HC; NuCort; Nutracort; Orabase HCA; Pandel; Penecort; Procort†; Proctocort; Proctocream HC 2.5%†; Recort Plus; Rectacort-HC; Scalacort DK; Solu-Cortef; Synacort; Tegrin-HC; Texacort; U-Cort; Westcort; Xerese; ***Venez.***: Corticina; Efficort; Hidrocort; Hidrozona; Liocort; Nutracort; Solu-Cortef; Stricort.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Gentamicin and Hydrocortisone Acetate Ear Drops; Hydrocortisone Acetate and Neomycin Ear Drops; Hydrocortisone Acetate and Neomycin Eye Drops; Hydrocortisone Acetate and Neomycin Eye Ointment; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injection; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Oral Suspension; Hydrocortisone and Clioquinol Cream; Hydrocortisone and Clioquinol Ointment; Hydrocortisone and Neomycin Cream; Hydrocortisone Cream; Hydrocortisone Ointment; Hydrocortisone Oromucosal Tablets; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Phosphate Oral Solution; Hydrocortisone Sodium Succinate Injection; Miconazole and Hydrocortisone Acetate Cream; Miconazole and Hydrocortisone Cream; Miconazole and Hydrocortisone Ointment;

USP 36: Chloramphenicol and Hydrocortisone Acetate for Ophthalmic Suspension; Chloramphenicol, Polymyxin B Sulfate, and Hydrocortisone Acetate Ophthalmic Ointment; Clioquinol and Hydrocortisone Cream; Clioquinol and Hydrocortisone

Ointment; Colistin and Neomycin Sulfates and Hydrocortisone Acetate Otic Suspension; Hydrocortisone Acetate Cream; Hydrocortisone Acetate Injectable Suspension; Hydrocortisone Acetate Lotion; Hydrocortisone Acetate Ointment; Hydrocortisone Acetate Ophthalmic Ointment; Hydrocortisone Acetate Ophthalmic Suspension; Hydrocortisone and Acetic Acid Otic Solution; Hydrocortisone Butyrate Cream; Hydrocortisone Cream; Hydrocortisone Gel; Hydrocortisone Injectable Suspension; Hydrocortisone Lotion; Hydrocortisone Ointment; Hydrocortisone Rectal Suspension; Hydrocortisone Sodium Phosphate Injection; Hydrocortisone Sodium Succinate for Injection; Hydrocortisone Tablets; Hydrocortisone Valerate Cream; Hydrocortisone Valerate Ointment; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Cream; Neomycin and Polymyxin B Sulfates and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Ophthalmic Suspension; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Solution; Neomycin and Polymyxin B Sulfates and Hydrocortisone Otic Suspension; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin Zinc, and Hydrocortisone Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ointment; Neomycin and Polymyxin B Sulfates, Bacitracin, and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates, Gramicidin, and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Cream; Neomycin Sulfate and Hydrocortisone Acetate Lotion; Neomycin Sulfate and Hydrocortisone Acetate Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Ointment; Neomycin Sulfate and Hydrocortisone Acetate Ophthalmic Suspension; Neomycin Sulfate and Hydrocortisone Cream; Neomycin Sulfate and Hydrocortisone Ointment; Neomycin Sulfate and Hydrocortisone Otic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Acetate Ophthalmic Suspension; Oxytetracycline Hydrochloride and Hydrocortisone Ointment; Polymyxin B Sulfate and Hydrocortisone Otic Solution.

Isoflupredone Acetate *(BANM, USAN, rINNM)* ⊗

Acetato de isoflupredona; 9α-Fluoroprednisolone Acetate; Isoflupredona, acetato de; Isofluprédone, Acétate d'; Isoflupredoni Acetas; U-6013; Изофлупредона Ацетат.

9α-Fluoro-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-acetate.

$C_{23}H_{29}FO_6$=420.5

CAS — 338-95-4 (isoflupredone); 338-98-7 (isoflupredone acetate).

UNII — 55P9TUL75S.

Pharmacopoeias. In *US* for veterinary use only.

USP 36: (Isoflupredone Acetate). Protect from light.

Profile

Isoflupredone acetate is a corticosteroid that has been used for its topical glucocorticoid activity (p. 1597.1) in allergic rhinitis.

Isoflupredone is also employed in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Israel*: Proaf†.

Loteprednol Etabonate *(BANM, USAN, rINNM)* ⊗

CDDD-5604; Etabonato de loteprednol; HGP-1; Lotéprednol, Etabonate de; Loteprednol, etabonato de; Loteprednol Ethyl Carbonate; Loteprednoli Etabonas; P-5604; Лотепреднола Этабонат.

(11β,17α)-17-[(Ethoxycarbonyl)oxy]-11-hydroxy-3-oxoandrosta-1,4-diene-17-carboxylic acid chloromethyl ester.

$C_{24}H_{31}ClO_7$=467.0

CAS — 129260-79-3 (loteprednol); 82034-46-6 (loteprednol etabonate).

ATC — S01BA14.

ATC Vet — QS01BA14.

UNII — YEH1EZ96K6.

Profile

Loteprednol etabonate is a corticosteroid used for its glucocorticoid activity (p. 1597.1) in the topical management of inflammatory and allergic disorders of the eye. It is usually used as eye drops containing 0.2 or 0.5%.

Prolonged application to the eye of preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

References.

1. Noble S, Goa KL. Loteprednol etabonate: clinical potential in the management of ocular inflammation. *BioDrugs* 1998; **10**: 329–39.
2. Pavesio CE, DeCory HH. Treatment of ocular inflammatory conditions with loteprednol etabonate. *Br J Ophthalmol* 2008; **92**: 455–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alrex; Lopred; Lotemax; Lotesoft; Talof; *Austria*: Lotemax; *Braz.*: Alrex; Loteprol; *Canad.*: Alrex; Lotemax; *Chile*: Oftol; *China*: Lotemax (露达舒); *Ger.*: Lotemax; *Gr.*: Lotemax; *Hong Kong*: Alrex; Lotemax; *India*: Loteflam; Lotepred; *Irl.*: Lotemax; *Israel*: Lotemax; *Ital.*: Lotemax; *Mex.*: Loterex; Lotesoft; *Pol.*: Lotemax; *Singapore*: Lotemax; *Thai.*: Lotemax; *Turk.*: Lotemax; *UK*: Lotemax; *USA*: Alrex; Lotemax; *Venez.*: Lotesoft.

Multi-ingredient Preparations. *Arg.*: Lotemicin; Zylet; *Braz.*: Zylet; *Israel*: Zylet; *Mex.*: Zyleth; *Singapore*: Zylet; *Thai.*: Zylet; *USA*: Zylet.

Mazipredone *(rINN)* ⊗

Mazipredona; Maziprédone; Mazipredonum; Мазипредон.

11β,17-Dihydroxy-21-(4-methyl-1-piperazinyl)pregna-1,4-diene-3,20-dione.

$C_{26}H_{38}N_2O_4$=442.6

CAS — 13085-08-0.

UNII — QN0W2YSW63.

Profile

Mazipredone is a corticosteroid used topically for its glucocorticoid activity (p. 1597.1). It is used as the hydrochloride with miconazole in the treatment of fungal infections of the skin.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Depersolon (Деперзолон).

Multi-ingredient Preparations. *Hung.*: Mycosolon; *Pol.*: Mycosolon; *Rus.*: Mycosolon (Микозолон); *Ukr.*: Mycosolon (Микозолон)†.

Meprednisone *(USAN, rINN)* ⊗

Meprednisona; Méprednisone; Meprednisonum; 16β-Methylprednisone; NSC-527579; Sch-4358; Мепреднизон.

17α,21-Dihydroxy-16β-methylpregna-1,4-diene-3,11,20-trione.

$C_{22}H_{28}O_5$=372.5

CAS — 1247-42-3.

ATC — H02AB15.

ATC Vet — QH02AB15.

UNII — 67U96J8P35.

Pharmacopoeias. In *US*.

USP 36: (Meprednisone). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Meprednisone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It has been given orally as either the free alcohol or the acetate and by injection as the sodium hemisuccinate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cortipyren B; Deltisona B; Latisona B†; Prednisonal; Prenolone; Rupesona B; *Mex.*: Lectan.

Methylprednisolone *(BAN, rINN)* ⊗

Meilprednizolon; Methylprednisolon; 6α-Methylprednisolone; Méthylprednisolone; Methylprednisolonum; Metilprednisolona; Metilprednizolon; Metilprednizolonas; Metylprednisolon; Metyyliprednisoloni; NSC-19987; Метилпреднизолон.

11β,17α,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione.

$C_{22}H_{30}O_5$=374.5

CAS — 83-43-2.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QD10AA02; QH02AB04.

UNII — X4W7ZR7023.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Methylprednisolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol; slightly soluble in acetone and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

USP 36: (Methylprednisolone). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 100 of alcohol, and in 1 in 800 of chloroform and of ether; slightly soluble in acetone; sparingly soluble in dioxan and in methyl alcohol. Store in airtight containers. Protect from light.

Methylprednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de metilprednisolona; Methylprednisolonacetat; Methylprednisolon-acetát; Méthylprednisolone, acétate de; Methylprednisoloni Acetas; Metilprednisolona, acetato de; Metilprednizolon Asetat; Metilprednizolon-acetát; Metilprednizolono acetatas; Metylprednisolonacetat; Metyyliprednisoloniasetaatti; Метилпреднизолона Ацетат.

Methylprednisolone 21-acetate.

$C_{24}H_{32}O_6$=416.5

CAS — 53-36-1.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — 43502P7F0P.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Methylprednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in alcohol and in acetone. Protect from light.

USP 36: (Methylprednisolone Acetate). A white or practically white, odourless, crystalline powder. Soluble 1 in 1500 of water, 1 in 400 of alcohol, 1 in 250 of chloroform, and 1 in 1500 of ether; sparingly soluble in acetone and in methyl alcohol; soluble in dioxan. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Methylprednisolone Hydrogen Succinate *(BANM, rINNM)* ⊗

Hidrogenosuccinato de metilprednisolona; Methylprednisolone Hemisuccinate; Méthylprednisolone, Hémisuccinate de; Méthylprednisolone, Hydrogénosuccinate de; Methylprednisolonhydrogensuccinat; Methylprednisolon-hydrogensukcinát; Methylprednisoloni Hemisuccinas; Methylprednisoloni Hydrogenosuccinas; Metilprednisolona, hidrogenosuccinato de; Metilprednizolon-hidrogén-szukcinát; Metilprednizolono vandenilio sukcinatas; Metylprednisolonvätesuccinat; Metyyliprednisolonivetysuksinaatti; Метилпреднизолона Гемисукцинат.

Methylprednisolone 21-(hydrogen succinate).

$C_{26}H_{34}O_8$=474.6

CAS — 2921-57-5.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — 5GMR90S4KN.

Pharmacopoeias. In *Eur.* (see p. vii); *Jpn*, and *US*.

Ph. Eur. 8: (Methylprednisolone Hydrogen Succinate). A white or almost white, hygroscopic powder. Practically insoluble in water; slightly soluble in dehydrated alcohol and in acetone; dissolves in dilute solutions of alkali hydroxides. Store in airtight containers. Protect from light.

USP 36: (Methylprednisolone Hemisuccinate). A white or nearly white, odourless or nearly odourless, hygroscopic solid. Very slightly soluble in water; freely soluble in alcohol; soluble in acetone. Store in airtight containers.

Methylprednisolone Sodium Succinate *(BANM, rINNM)* ⊗

Methylprednisolone Sodium Hemisuccinate; Méthylprednisolone, Succinate Sodique de; Methylprednisoloni Natrii Succinas; Metilprednisolona, succinato sódico de; Metilprednizolon Sodyum Süksinat; Succinato sódico de metilprednisolona; Метилпреднизолона Натрия Сукцинат.

Methylprednisolone 21-(sodium succinate).

$C_{26}H_{33}NaO_8$=496.5

CAS — 2375-03-3.

ATC — D07AA01; H02AB04.

ATC Vet — QD07AA01; QH02AB04.

UNII — LEC9GKY20K.

Pharmacopoeias. In *US*.

USP 36: (Methylprednisolone Sodium Succinate). A white or nearly white, odourless, hygroscopic, amorphous solid. Soluble 1 in 1.5 of water and 1 in 12 of alcohol; very slightly soluble in acetone; insoluble in chloroform and in ether. Store in airtight containers. Protect from light.

Stability. Methylprednisolone sodium succinate injection (*Solu-Medrol, USA*) was considered to be stable for 7 days when diluted in water for injection and stored in glass vials at 4 degrees. When stored under similar conditions at 22 degrees, it was considered to be stable for 24 hours.[1] The manufacturers state that the prepared solution should be stored at 20 to 25 degrees and used within 48 hours of mixing.

1. Nahata MC, *et al.* Stability of diluted methylprednisolone sodium succinate injection at two temperatures. *Am J Hosp Pharm* 1994; 51: 2157–9.

Uses and Administration

Methylprednisolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 4 mg of methylprednisolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone.

It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p. 1597.3) except adrenocortical-deficiency states, for which hydrocortisone with supplementary fludrocortisone is preferred.

The dose is usually expressed in terms of the base, and the following are each equivalent to about 40 mg of methylprednisolone:

- methylprednisolone acetate 44 mg
- methylprednisolone hydrogen succinate 51 mg
- methylprednisolone sodium succinate 53 mg

However, esterification generally alters potency and compounds with equivalent methylprednisolone content may not have equivalent clinical effect.

When given **orally**, methylprednisolone usually has an initial dosage range of 4 to 48 mg daily but higher initial doses of up to 100 mg or more daily may be used in acute severe disease.

For **parenteral use** in *intensive* or *emergency therapy*, methylprednisolone sodium succinate may be given by intramuscular or intravenous injection or by intravenous infusion. The intravenous route is preferred for its more rapid effect in emergency therapy. The usual initial intramuscular or intravenous dose ranges from the equivalent of 10 to 500 mg of methylprednisolone daily. Large intravenous doses (over 250 mg) should normally be given slowly over at least 30 minutes; doses up to 250 mg should be given over at least 5 minutes. High doses should generally not be given for prolonged periods; emergency treatment should only be used until the patient is stabilised. High doses given intermittently for a limited period have sometimes been known as 'pulse therapy' (see Administration, below) and in *graft rejection* (see Organ and Tissue Transplantation, p. 1932.2) up to 1 g has been given daily for up to 3 days. In intensive therapy of acute *spinal cord injury* (p. 1613.2) initial doses of the equivalent of 30 mg/kg of methylprednisolone have been given by bolus intravenous injection over 15 minutes and followed, after a 45-minute pause, by intravenous infusion of 5.4 mg/kg per hour over 24 hours or longer. For slow intravenous infusion methylprednisolone sodium succinate is dissolved in an appropriate volume of glucose 5% or sodium chloride 0.9% or sodium chloride 0.9% and glucose 5%.

For doses used in children, see below.

Methylprednisolone acetate may be given as an aqueous suspension by intramuscular injection for a prolonged systemic effect, the dose varying from 40 mg every 2 weeks to 120 mg weekly.

For **intra-articular injection** and for **injection into soft tissues** methylprednisolone acetate aqueous suspension is used. The dose by intra-articular injection varies from 4 to 80 mg according to the size of the affected joint. The acetate may also be given by intralesional injection in doses of 20 to 60 mg.

For use in the treatment of various skin disorders methylprednisolone acetate may be applied **topically**, usually in concentrations of 0.25%. The aceponate, which may show modified topical activity, has also been applied as a 0.1% cream, lotion, or ointment. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Other esters of methylprednisolone that have occasionally been used include the cipionate and the suleptanate.

General references.

1. Cronstein BN. Clinical use of methylprednisolone sodium succinate: a review. *Curr Ther Res* 1995; 56: 1–15.

Administration. For short-term intensive corticosteroid therapy or in certain emergency situations a technique known as 'pulse therapy' has been used. Methylprednisolone has often been used in this manner. Typically, high doses of about 1 g intravenously have been given, daily or on alternate days or weekly, for a limited number of doses; the most common regimen appears to be 1 g daily for 3 days.

Administration in children. Doses of methylprednisolone in children have varied considerably, depending on the condition being treated.

The *BNFC* suggests that an oral dose of 0.5 to 1.7 mg/kg daily in 2 to 4 divided doses may be used for inflammatory and allergic disorders in children aged from 1 month to 18 years old.

Methylprednisolone sodium succinate has been given **parenterally** by the intravenous route. The *BNFC* suggests that inflammatory and allergic disorders may be treated intravenously, by either injection or infusion, in equivalent doses to those used orally. High intravenous doses providing 10 to 30 mg/kg (maximum 1 g) of methylprednisolone, given once daily or on alternate days for up to 3 doses, may be used in 'pulse therapy' in children aged from 1 month to 18 years old for conditions such as severe erythema multiforme (Stevens-Johnson syndrome), lupus nephritis, and systemic onset juvenile idiopathic arthritis. In graft rejection, a dose of 10 to 20 mg/kg (maximum 1 g) once daily may be given for up to 3 days.

Blood disorders. Methylprednisolone is one of the corticosteroids that have been used in the management of haemangioma (p. 1605.3) and the Kasabach-Merritt syndrome.[1] There are also reports of benefit from very high-dose therapy in a few patients with refractory primary acquired pure red cell aplasia,[2] or aplasia due to Blackfan-Diamond anaemia.[3]

1. Özsoylu Ş, *et al.* Megadose methylprednisolone therapy for Kasabach-Merritt syndrome. *J Pediatr* 1996; 129: 947.
2. Kadikoylu G, *et al.* High-dose methylprednisolone therapy in pure red cell aplasia. *Ann Pharmacother* 2002; 36: 55–8.
3. Bernini JC, *et al.* High-dose intravenous methylprednisolone therapy for patients with Diamond-Blackfan anemia refractory to conventional doses of prednisone. *J Pediatr* 1995; 127: 654–9.

IMMUNE THROMBOCYTOPENIA. High-dose intravenous methylprednisolone may be used as part of the emergency management of immune thrombocytopenia (p. 1606.1), for example when major acute bleeding or intracranial haemorrhage supervene. There is some evidence that methylprednisolone is less effective than normal immunoglobulins. Methylprednisolone has also been used orally or intravenously in the management of the chronic form, although prednisolone or prednisone are more frequently used for oral therapy and good controlled studies are scanty.

References.

1. von dem Borne AEGKR, *et al.* High dose intravenous methylprednisolone or high dose intravenous gammaglobulin for autoimmune thrombocytopenia. *BMJ* 1988; 296: 249–50.
2. Özsoylu S, *et al.* Megadose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1990; 336: 1078–9.
3. Akoğlu T, *et al.* Megadose methylprednisolone pulse therapy in adult idiopathic thrombocytopenic purpura. *Lancet* 1991; 337: 56.
4. Özsoylu S. Mega-dose methylprednisolone for chronic idiopathic thrombocytopenic purpura. *Lancet* 1991; 337: 1611–12.
5. Rosthøj S, *et al.* Randomized trial comparing intravenous immunoglobulin with methylprednisolone pulse therapy in acute idiopathic thrombocytopenic purpura. *Acta Paediatr* 1996; 85: 910–15.
6. Alpdoğan Ö, *et al.* Efficacy of high-dose methylprednisolone as a first-line therapy in adult patients with idiopathic thrombocytopenic purpura. *Br J Haematol* 1998; 103: 1061–3.
7. Godeau B, *et al.* Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; 359: 23–9.

Rheumatoid arthritis. Methylprednisolone given in intravenous pulses has been reported[1-7] to be effective in the treatment of rheumatoid arthritis (p. 13.2) including juvenile idiopathic arthritis. Some studies have shown this treatment to be of greatest benefit when given with a disease-modifying antirheumatic drug (DMARD),[1,2,4] although others showed the addition of methylprednisolone to existing therapy to have no extra benefit.[6] A comparatively low dose of 100 mg was found to be as effective as 1 g in one study.[3] Monthly doses of methylprednisolone by deep intramuscular injection were also an effective adjunct to gold therapy.[8]

A preliminary study in children has found intravenous pulses of methylprednisolone 30 mg/kg to be effective treatment for systemic flares of juvenile idiopathic arthritis.[7]

1. Walters HT, Gawley MID. Combined suppressive drug treatment in severe refractory rheumatoid disease: an analysis of the relative effects of parenteral methylprednisolone, cyclophosphamide and sodium aurothiomalate. *Ann Rheum Dis* 1988; 47: 924–9.
2. Smith MD, *et al.* The clinical and immunological effects of pulse methylprednisolone therapy in rheumatoid arthritis I: clinical effects. *J Rheumatol* 1988; 15: 229–32.
3. Igelhart IW, *et al.* Intravenous pulsed steroids in rheumatoid arthritis: a comparative dose study. *J Rheumatol* 1990; 17: 159–62.
4. Smith MD, *et al.* Pulse methylprednisolone therapy in rheumatoid arthritis: unproved therapy, unjustified therapy, or effective adjunctive treatment? *Ann Rheum Dis* 1990; 49: 265–7.
5. Kapisinszky N, Keszthelyi B. High dose intravenous methylprednisolone pulse therapy in patients with rheumatoid arthritis. *Ann Rheum Dis* 1990; 49: 567–8.
6. Hansen TM, *et al.* Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. *BMJ* 1990; 301: 268–70.
7. Adebajo AO, Hall MA. The use of intravenous pulsed methylprednisolone in the treatment of systemic-onset juvenile chronic arthritis. *Br J Rheumatol* 1998; 37: 1240–2.
8. Corkill MM, *et al.* Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. *Br J Rheumatol* 1990; 29: 274–9.

Systemic lupus erythematosus. Methylprednisolone has been widely used to treat disease flares or severe manifestations of SLE (p. 1613.3).

References.

1. Badsha H, Edwards CJ. Intravenous pulses of methylprednisolone for systemic lupus erythematosus. *Semin Arthritis Rheum* 2003; 32: 370–7.
2. Danowski A, *et al.* Flares in lupus: Outcome Assessment Trial (FLOAT), a comparison between oral methylprednisolone and intramuscular triamcinolone. *J Rheumatol* 2006; 33: 57–60.
3. Trevisani VF, *et al.* Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 20/06/06).

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). Rapid intravenous injection of large doses has been associated with cardiovascular collapse.

Methylprednisolone may be slightly less likely than prednisolone to cause sodium and water retention.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

References to various adverse effects associated with intravenous methylprednisolone in high-dose pulse therapy[1-11] and to adverse effects after intra-articular[12,13] and intranasal injection.[14] Epidural dosage (or more particularly inadvertent intrathecal dosage during attempted epidural placement) may be associated with serious adverse effects including arachnoiditis and aseptic meningitis, although the degree of risk is uncertain.[15]

1. Newmark KJ, *et al.* Acute arthralgia following high-dose intravenous methylprednisolone therapy. *Lancet* 1974; ii: 229.
2. Bailey RR, Armour P. Acute arthralgia after high-dose intravenous methylprednisolone. *Lancet* 1974; ii: 1014.
3. Bennett WM, Strong D. Arthralgia after high-dose steroids. *Lancet* 1975; i: 332.
4. Moses RE, *et al.* Fatal arrhythmia after pulse methylprednisolone therapy. *Ann Intern Med* 1981; 95: 781–2.
5. Oto A, *et al.* Methylprednisolone pulse therapy and peritonitis. *Ann Intern Med* 1983; 99: 282.
6. Suchman AL, *et al.* Seizure after pulse therapy with methyl prednisolone. *Arthritis Rheum* 1983; 26: 117.
7. Ayoub WT, *et al.* Central nervous system manifestations after pulse therapy for systemic lupus erythematosus. *Arthritis Rheum* 1983; 26: 809–10.
8. Williams AJ, *et al.* Disseminated aspergillosis in high dose steroid therapy. *Lancet* 1983; i: 1222.
9. Barrett DF. Pulse methylprednisolone therapy. *Lancet* 1983; ii: 800.
10. Baethge BA, Lidsky MD. Intractable hiccups associated with high-dose intravenous methylprednisolone therapy. *Ann Intern Med* 1986; 104: 58–9.
11. Gardiner PVG, Griffiths ID. Sudden death after treatment with pulsed methylprednisolone. *BMJ* 1990; 300: 125.
12. Black DM, Filak AT. Hyperglycemia with non-insulin-dependent diabetes following intraarticular steroid injection. *J Fam Pract* 1989; 28: 462–3.
13. Pollock B, *et al.* Chronic urticaria associated with intra-articular methylprednisolone. *Br J Dermatol* 2001; 144: 1228–30.
14. Johns KJ, Chandra SR. Visual loss following intranasal corticosteroid injection. *JAMA* 1989; 261: 2413.
15. Rodgers PT, Connelly JP. Epidural administration of methylprednisolone for back pain. *Am J Hosp Pharm* 1994; 51: 2789–90.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methylprednisolone as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Methylprednisolone is fairly rapidly distributed after oral doses, with a plasma half-life of 3.5 hours or more. The tissue half-life is reported to range from 18 to 36 hours.

Methylprednisolone acetate is absorbed from joints over a week but is more slowly absorbed following deep intramuscular injection. The sodium succinate ester is rapidly absorbed after intramuscular doses, and peak plasma concentrations occur in 2 hours.

Methylprednisolone crosses the placenta.

References.

1. Tornatore KM, *et al.* Repeated assessment of methylprednisolone pharmacokinetics during chronic immunosuppression in renal transplant recipients. *Ann Pharmacother* 1995; 29: 120–4.
2. Rohatagi S, *et al.* Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; 37: 916–25.

3. Tornatore KM, *et al.* Pharmacokinetics and pharmacodynamic response of methylprednisolone in premenopausal renal transplant recipients. *J Clin Pharmacol* 2004; **44:** 1003–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Advantan; Cipridanol; Cortisolona; Solu-Medrol; Totalsolona; ***Austral.***: Advantan; Depo-Medrol; Depo-Nisolone; Methylpred; Solu-Medrol; ***Austria***: Advantan; Solu-Medrol; Urbason; ***Belg.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Braz.***: Advantan; Alergolon; Depo-Medrol; Predi-Medrol; Predmetil; Solu-Medrol; Solupren; Unimedrol; ***Canad.***: Depo-Medrol; Medrol; Solu-Medrol; ***Chile***: Depo-Medrol; Medrol; Solu-Medrol; ***China***: Medrol (美卓乐); Mi Le Song (米乐松); Solu-Medrol (甲强龙); You Jin (尤金); ***Cz.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***Denm.***: Depo-Medrol; Medrol; Solu-Medrol; ***Fin.***: Advantan; Depo-Medrol; Medrol; Solomet; Solu-Medrol; ***Fr.***: Depo-Medrol; Medrol; Solu-Medrol; ***Ger.***: Advantan; M-PrediHexal; Metypred; Metysolon; Predni M; Urbason; ***Gr.***: Advantan; Depo-Medrol; Depo-Medrone†; Fodier; Lyo-drol; Medrol; Solu-Medrol; Veriderm Medrol; ***Hong Kong***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Hung.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***India***: Acto-Pred; Aricort M; Avpred; Biolone; Cecort; Depo-Medrol; Depomax; Depopred; Deposet; Dispred; Elpred M; Geopred; Happisone; Hosicort; Ivepred; Lumi-M; Lupus; MB Sole; Medicort; Medrol; Mega-Pred; Melpred; Melsone; Mepred; Meprosol; Mepsonate; Methyl-Pred; MPA; MPSS; MSLone; Mypred; Nayapred; Neo-Drol; Neodrol-AS; Nicord; Nicort; Nispred; Omnacortil; Solu-Medrol; ***Indon.***: Advantan; Comedrol; Depo-Medrol; Flason; Glomeson; Hexilon; Intidrol; Lameson; Lexcomet; Medixon; Medrol; Meprilon; Meproson; Mesol; Metcor; Methylon; Metidrol†; Metisol; Metrison; Nichomedson; Phadilon; Prednicort; Prednox; Pretilon; Prolon 8; Rhemafar; Sanexon; Solu-Medrol; Somerol; Sonicor; Stenirol; Thimelon; Tisolon; Tison; Toras; Tropidrol; Urbason; Xilon; Yalone; ***Irl.***: Advantan; Depo-Medrone; Solu-Medrone; ***Israel***: Depo-Medrol; Medrol; Solu-Medrol; ***Ital.***: Advantan; Asmacortone†; Avancort†; Depo-Medrol; Medrol; Metilbetasone Solubile†; Solu-Medrol; Supresol; Urbason; ***Malaysia***: Depo-Medrol; Solu-Medrol; ***Mex.***: Advantan; Cryosolona; Depo-Medrol; Metisona; Prednilem†; Radilem†; Solipred; Solu-Medrol; ***Neth.***: Depo-Medrol; Solu-Medrol; ***Norw.***: Depo-Medrol; Medrol; Solu-Medrol; ***NZ***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Philipp.***: Adrena; Advantan; Depo-Medrol; Medixon; Medrol; Mepresone; Prednox; Solu-Medrol; Solu-Ped; Solucin; ***Pol.***: Advantan; Depo-Medrol; Medrol; Metypred; Solu-Medrol; ***Port.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Rus.***: Advantan (Адвантан); Depo-Medrol (Депо-медрол); Lemod (Лемод); Medrol (Медрол); Metypred (Метипред); Solu-Medrol (Солу-медрол); ***S.Afr.***: Advantan; AP Methylpred; Depo-Medrol; Medrol; Metypresol†; Solu-Medrol; ***Singapore***: Solu-Medrol; ***Spain***: Adventan; Lexxema; Solu-Moderin; Urbason; ***Swed.***: Depo-Medrol; Medrol; Solu-Medrol; ***Switz.***: Advantan; Depo-Medrol; Medrol; Solu-Medrol; ***Thai.***: Depo-Medrol; Solu-Medrol; ***Turk.***: Advantan; Depo-Medrol; Depometikort; Precort; Prednol; Urbason; ***UK***: Depo-Medrone; Medrone; Solu-Medrone; ***Ukr.***: Advantan (Адвантан); Depo-Medrol (Депо-Медрол); Medrol (Медрол); Metypred (Метипред); Solu-Medrol (Солу-Медрол); Sterocort (Стерокорт); ***USA***: A-Methapred; dep-Medalone; Depo-Medrol; Medrol; Solu-Medrol; ***Venez.***: Advantan; Depo-Medrol; Medrol; Prednicort; Solu-Medrol.

Multi-ingredient Preparations. ***Austral.***: Neo-Medrol†; ***Belg.***: Depo-Medrol + Lidocaine; ***Canad.***: Depo-Medrol with Lidocaine; Medrol Acne Lotion; Neo-Medrol Acne; ***Fin.***: Depo-Medrol cum Lidocain; Solomet c bupivacain hydrochlorid; ***Gr.***: Medrol Acne Lotion; Neo-Medrol; Veriderm-Neo Medrol; ***Hong Kong***: Depo-Medrol with Lidocaine; Neo-Medrol Acne; ***Irl.***: Depo-Medrone with Lidocaine; ***Israel***: Depo-Medrol with Lidocaine; Neo-Medrol; ***Ital.***: Depo-Medrol + Lidocaina; ***Malaysia***: Neo-Medrol; ***Neth.***: Depo-Medrol + Lidocaine; ***Norw.***: Depo-Medrol cum Lidocain; ***NZ***: Depo-Medrol with Lidocaine; ***Pol.***: Depo-Medrol z Lidokaina; ***Port.***: Depo-Medrol com Lidocaina; ***S.Afr.***: Depo-Medrol with Lidocaine; Neo-Medrol†; ***Singapore***: Neo-Medrol; ***Swed.***: Depo-Medrol cum Lidocain; ***Switz.***: Depo-Medrol Lidocaine; ***Thai.***: Neo-Medrol; ***UK***: Depo-Medrone with Lidocaine.

Pharmacopoeial Preparations

BP 2014: Methylprednisolone Acetate Injection; Methylprednisolone Tablets;

USP 36: Methylprednisolone Acetate Cream; Methylprednisolone Acetate Injectable Suspension; Methylprednisolone Sodium Succinate for Injection; Methylprednisolone Tablets; Neomycin Sulfate and Methylprednisolone Acetate Cream.

Mometasone Furoate

(BANM, USAN, rINNM) ⊗

Furoato de mometasona; Mometasona, furoato de; Mométasone, furoate de; Mometasonfuroat; Mometasonfuróat; Mometasoni Furoas; Mometasonifuroaatti; Mometazon Furoat; Mometazon-furoát; Mometazono furoatas; Mometazonu furoinian; Sch-32088; Мометазона фуроат.

9α,21-Dichloro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione 17-(2-furoate).

$C_{27}H_{30}Cl_2O_6$=521.4

CAS — 105102-22-5 (mometasone); 83919-23-7 (mometasone furoate).

ATC — D07AC13; R01AD09; R03BA07.

ATC Vet — QD07AC13; QR01AD09; QR03BA07.

UNII — 04201GDN4R.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Mometasone Furoate). A white or almost white powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone and in dichloromethane.

USP 36: (Mometasone Furoate). A white to off-white powder. Soluble in acetone and in dichloromethane.

Uses and Administration

Mometasone furoate is a corticosteroid used for its glucocorticoid activity (see p. 1597.1).

Mometasone furoate is used by dry powder inhaler for the prophylaxis of **asthma** (below). Doses may differ between countries and dosage units may be expressed differently, as either the amount of drug released per actuation or the amount delivered from the mouthpiece. UK licensed product information includes an initial dose of 400 micrograms inhaled once daily in the evening for mild to moderate asthma in adults and adolescents aged 12 years and older. This may be adjusted to a maintenance dose of 200 micrograms once or twice daily. In severe asthma, an initial dose of 400 micrograms twice daily is used, then titrated to the lowest effective dose once symptoms are controlled. US doses are provided in terms of the amount of drug released per actuation (an actuation that releases 110 micrograms delivers 100 micrograms from the mouthpiece). An initial dose of 220 micrograms once daily in the evening is used in adults and adolescents, aged 12 years and older, who have been treated with inhaled therapy only (bronchodilators or corticosteroids); this may be increased to a maximum of 440 micrograms daily as a single dose or 2 divided doses. Patients receiving oral corticosteroids may be started on 440 micrograms twice daily.

A nasal suspension of mometasone furoate 0.05%, as the monohydrate, is given in the treatment and prophylaxis of the symptoms of **allergic rhinitis** (below). The usual dose is the equivalent of 100 micrograms of mometasone furoate in each nostril once daily, increased if necessary to 200 micrograms in each nostril daily. Once symptoms are controlled a dose of 50 micrograms in each nostril daily may be effective for maintenance.

The nasal suspension is also given for the treatment of **nasal polyps** (below) in patients 18 years and older; the recommended initial dose in the UK is 100 micrograms into each nostril once daily, increased after 5 to 6 weeks to twice daily if needed. In the USA the recommended initial dose is 100 micrograms in each nostril twice daily, although once daily administration may be sufficient in some patients.

Mometasone furoate is used topically in the treatment of various **skin disorders** (below). It is usually used as a cream, ointment, lotion, or scalp application containing 0.1%. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

For doses used in children, see below.

Administration in children. Mometasone furoate may be used in the management of **asthma** in children. In the USA, a dry powder inhaler is licensed for use in children aged 4 to 11 years in a dose of 110 micrograms once daily in the evening, regardless of prior therapy; this is the maximum recommended daily dose.

A nasal suspension of mometasone furoate 0.05%, as the monohydrate, is given in the treatment of the symptoms of **allergic rhinitis**. In the UK, the dose for children aged between 6 and 11 years is the equivalent of 50 micrograms in each nostril once daily. In the USA, similar doses may be given to children as young as 2 years of age.

Older children are given adult doses for these indications (see above).

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3). Reviews of the use of mometasone furoate.

1. Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. *Drugs* 2001; **61:** 1325–50.
2. McCormack PL, Plosker GL. Inhaled mometasone furoate: a review of its use in persistent asthma in adults and adolescents. *Drugs* 2006; **66:** 1151–68.

Nasal polyps. For discussion of the value of corticosteroids in the treatment of nasal polyps, see p. 1608.2. References to the use of mometasone furoate.

1. Stjärne P, *et al.* A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 2006; **132:** 179–85.
2. Stjärne P, *et al.* The efficacy and safety of once-daily mometasone furoate nasal spray in nasal polyposis: a randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2006; **126:** 606–12.
3. Small CB, *et al.* Onset of symptomatic effect of mometasone furoate nasal spray in the treatment of nasal polyposis. *J Allergy Clin Immunol* 2008; **121:** 928–32.
4. Stjärne P, *et al.* Use of mometasone furoate to prevent polyp relapse after endoscopic sinus surgery. *Arch Otolaryngol Head Neck Surg* 2009; **135:** 296–302.

Rhinitis. For a discussion of the management of rhinitis, including the use of corticosteroids, see p. 612.1. Some further references to the use of mometasone furoate in rhinitis are given below.

1. Onrust SV, Lamb HM. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 1998; **56:** 725–45.
2. Lundblad L, *et al.* Mometasone furoate nasal spray in the treatment of perennial non-allergic rhinitis: a Nordic, multicenter, randomized, double-blind, placebo-controlled study. *Acta Otolaryngol* 2001; **121:** 505–9.
3. Schenkel E. Features of mometasone furoate nasal spray and its utility in the management of allergic rhinitis. *Expert Opin Pharmacother* 2003; **4:** 1579–91.
4. van Drunen C, *et al.* Nasal allergies and beyond: a clinical review of the pharmacology, efficacy, and safety of mometasone furoate. *Allergy* 2005; **60** (suppl 80): 5–19. Correction. *ibid.*; 1335.
5. Zitt M, *et al.* Mometasone furoate nasal spray: a review of safety and systemic effects. *Drug Safety* 2007; **30:** 317–26.
6. Baldwin GM, Scott LJ. Mometasone furoate: a review of its intranasal use in allergic rhinitis. *Drugs* 2008; **68:** 1723–39.

Skin disorders. References.

1. Prakash A, Benfield P. Topical mometasone: a review of its pharmacological properties and therapeutic use in the treatment of dermatological disorders. *Drugs* 1998; **55:** 145–63.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Adrenal suppression may occur in some patients treated with high-dose long-term inhalation of mometasone furoate for asthma. Systemic absorption may also follow nasal use, particularly after high doses or prolonged treatment.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies mometasone as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 04/11/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3. Mometasone furoate is poorly absorbed after inhalation, intranasal use, and topical application. It undergoes hepatic metabolism mainly by the cytochrome P450 isoenzyme CYP3A4. The terminal elimination half-life is about 5 hours; metabolites are excreted mainly in the faeces and to a lesser extent in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Derimod; Elocon; Fenisona; Hexaler Bronquial; Hexaler Nasal; Metason; Momeplus; Mometax; Nasonex; Novasone; Uniclar; ***Austral.***: Elocon; Nasonex; Novasone; ***Austria***: Asmanex; Elocon; Nasonex; ***Belg.***: Elocom; Nasonex; ***Braz.***: Dermotil; Elocom; Nasonex; Oximax; Topison; Topliv; ***Canad.***: Asmanex; Elocom; Nasonex; ***Chile***: Dermaten; Dermosona; Elocom; Flogocort; Lisoder; Metacross; Momelab; Nasonex; Rinoval; Uniclar; ***China***: Eloson (艾洛松); Pu Mei Song (美美松); Nasonex (内舒拿); Suqi (速奇); ***Cz.***: Asmanex; Elocom; Eztom; Momerid; Nasonex; ***Denm.***: Asmanex; Elocom; Elocon; Nasomet; Nasonex; ***Fin.***: Asmanex; Demoson; Elocon; Nasonex; ***Fr.***: Nasonex; ***Ger.***: Asmanex; Ecural; Momegalen; Nasonex; ***Gr.***: Asmanex; Bioelementa; Ecelecort; Elocon; Elovent; Esine; F-Din; Fremomet; Logren; Makiren; Metason; Mofur; Molken; Momecort; Movesan; Mozeton; Nasamet; Nasonex; Pharmecort; Prospiril; Yperod; ***Hong Kong***: Elisone; Elomet; Elosone; Nasonex; Topcort; ***Hung.***: Elocom; Momegen; Nasonex; ***India***: Aquamet; Cratisone; Cumef; Cutizone; Dermanex; Elocon; Ezoma; Femcort; HHSone; M-Fact; Metacon; Metacort; Metaspray; Mezo; MMS; Moco; Momate; Momecon; Momeflo; Momoz; Momtas; Most; Topcort; ***Indon.***: Dermovel; Elocon; Eloskin; Elox; Iflacort; Intercon; Mefurosan; Mesone; Metaflam; Mofacort; Mofulex; Momet; Motaderm; Moteson†; Nasonex; ***Irl.***: Asmanex; Elocon; Monovo; Nasonex; ***Israel***: Elocom; Nasonex; ***Ital.***: Altosone; Elocon; Nasonex; Rinelon; ***Jpn***: Nasonex; ***Malaysia***: Elomet; Elosone; Melomet; Momate; Nasonex; Vizomet; ***Mex.***: Elica; Elomet; Elovent; Rinelon; Uniclar; ***Neth.***: Asmanex; Elocon; Elovent†; Monovo; Nasonex; ***Norw.***: Asmanex; Elocon; Nasonex; ***NZ***: Asmanex†; Bronconex;

Elocon; Nasonex; *Philipp.*: Elica; Elocon; Mezo; Momate; Mosone; Nasonex; Rinelon; *Pol.*: Asmanex; Elocom; Elosone; Momarid; Momederm; Nasonex; *Port.*: Asmanex; Desdek; Elocom; Elomet; Elovent; Nasomet; Prospiril; *Rus.*: Elocom (Элоком); Momat (Момат); Nasonex (Назонекс); Uniderm (Унидерм); *S.Afr.*: Elocon; Mometagen; Nasonex; Nexomist; Rinelon; *Singapore*: Asmanex; Elomet; Elosone; Nasonex; *Spain*: Asmanex; Elica; Elocom; Konex; Nasonex; Pinarsina†; Rinelon†; *Swed.*: Asmanex; Demoson; Elocon; Nasonex; *Switz.*: Asmanex; Elocom; Monovo; Nasonex; *Thai.*: Elomet; Nasonex; Novasone; Rinelon; *Turk.*: Asmanex; Codermo; Elocon; M-Furo; Momecon; Mometix; Nasonex; Nazofix; Nazoster; Rinose; Risonel; *UK*: Asmanex; Elocon; Nasonex; *Ukr.*: Elocom (Элоком); Eloson (Элозон); Momederm (Момедерм); Nasonex (Назонекс); *USA*: Asmanex; Elocon; Momexin; Nasonex; Propel; *Venez.*: Asmanex; Cortynase; Dergentil; Elocon; Elomet; Nasonex.

Multi-ingredient Preparations. *Canad.*: Zenhale; *Chile*: Velosalic†; *Cz.*: Momesalic; *Ger.*: Elosalic; *Gr.*: Elosalic; Momesalic; *Hong Kong*: Elosalic; *Hung.*: Elosalic; *India*: Cortimax-S; Cutizone-T; Depig-TM; Eveglow; Fudec-M; Furomet; M-Lite; Mecloma-P; Mecloma-T; Melacare; Melacut; Melalite-XL; Metazole; Mezo-T; Momate-S; Momoz-F; Momoz-S; Momoz-T; Motoso; Multi-HTM; *Indon.*: Elosalic; *Pol.*: Elosalic; *Port.*: Monsalic; *Rus.*: Elocom-S (Элоком-С); Momat-S (Момат-С); *S.Afr.*: Elosalic†; *Singapore*: Elosalic; *Spain*: Elocom Plus; *Swed.*: Elosalic; *Turk.*: Elosalic; Momesalic; *Ukr.*: Elocom-S (Элоком-С); *USA*: Dulera; *Venez.*: Elosalic.

Pharmacopoeial Preparations
BP 2014: Mometasone Aqueous Nasal Spray; Mometasone Cream; Mometasone Ointment; Mometasone Scalp Application; **USP 36:** Mometasone Furoate Cream; Mometasone Furoate Ointment; Mometasone Furoate Topical Solution.

Paramethasone Acetate

(BANM, USAN, rINNM) ⊗

Acetato de parametasona; 6α-Fluoro-16α-methylprednisolone 21-Acetate; Parametasona, acetato de; Parametazon Asetat; Paraméthasone, Acétate de; Parmethasoni Acetas; Параметазона Ацетат.

6α-Fluoro-11β,17α,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate.

$C_{24}H_{31}FO_6$=434.5

CAS — 53-33-8 (paramethasone); 1597-82-6 (paramethasone acetate).

ATC — H02AB05.

ATC Vet — QH02AB05.

UNII — 8X50N88ZDP.

Pharmacopoeias. In *Fr.*

Profile

Paramethasone acetate is a corticosteroid that has been used systemically for its mainly glucocorticoid activity (p. 1597.1); 2 mg of paramethasone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. The disodium phosphate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Dilar; *Mex.*: Dilar†; *Turk.*: Depo-Dilar.

Multi-ingredient Preparations. *Mex.*: Dilarmine†.

Prednicarbate *(BAN, USAN, rINN)* ⊗

Hoe-777; Prednicarbat; Prednicarbato; Prednicarbatum; Prednikarbaatti; Prednikarbat; Prednikarbát; Prednikarbatas; S-77-0777; Предникарбат.

11β,17,21-Trihydroxypregna-1,4-diene-3,20-dione 17-(ethyl carbonate) 21-propionate.

$C_{27}H_{36}O_8$=488.6

CAS — 73771-04-7.

ATC — D07AC18.

ATC Vet — QD07AC18.

UNII — V901LV1K7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Prednicarbate). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

USP 36: (Prednicarbate). A white to almost white crystalline powder. Practically insoluble in water; freely soluble in alcohol and in acetone; sparingly soluble in propylene glycol. Protect from light.

Profile

Prednicarbate is a corticosteroid used topically for its glucocorticoid activity (see p. 1597.1) in the treatment of various skin disorders. It has usually been used as a cream, ointment, or lotion, containing 0.1 to 0.25%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (see p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

References.

1. Schäfer-Korting M, *et al.* Prednicarbate activity and benefit/risk ratio in relation to other topical glucocorticoids. *Clin Pharmacol Ther* 1993; 54: 448–56.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednicarbate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Prednitop; *Braz.*: Dermatop; Invex; *Canad.*: Dermatop; *Chile*: Dermatop; *Cz.*: Dermatop; *Ger.*: Dermatop†; Prednitop; *India*: Dermatop; *Indon.*: Dermatop; *Ital.*: Dermatop; *Mex.*: Alisyd; *Spain*: Batmen; Peitel; *Switz.*: Prednicutan; Prednitop; *Thai.*: Dermatop; *Turk.*: Dermatop; *USA*: Dermatop.

Pharmacopoeial Preparations
USP 36: Prednicarbate Cream; Prednicarbate Ointment.

Prednisolone *(BAN, rINN)* ⊗

1,2-Dehydrohydrocortisone; Deltahydrocortisone; Metacortandralone; NSC-9120; Prednisolon; Prednisolona; Prednisoloni; Prednisolonum; Prednizolon; Prednizolonas; Преднизолон.

11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione.

$C_{21}H_{28}O_5$=360.4

CAS — 50-24-8 (anhydrous prednisolone); 52438-85-4 (prednisolone sesquihydrate).

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QD07XA02; QH02AB06; QR01AD02; QS01BA04; QS01CB02; QS02BA03; QS03BA02.

UNII — 9PHQ9Y1OLM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.*

US allows the anhydrous form or the sesquihydrate.

Ph. Eur. 8: (Prednisolone). A white or almost white, hygroscopic, crystalline powder. It shows polymorphism. Very slightly soluble in water; soluble in alcohol and in methyl alcohol; sparingly soluble in acetone; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Prednisolone). It is anhydrous or contains one and one-half molecules of water of hydration. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 30 of alcohol, 1 in 50 of acetone, and 1 in 180 of chloroform; soluble in dioxan and in methyl alcohol.

Prednisolone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisolona; Prednisolona, acetato de; Prednisolonacetat; Prednisolon-acetát; Prednisolone, acétate de; Prednisoloni Acetas; Prednisoloniasetaatti; Prednizolon Asetat; Prednizolon-acetát; Prednizolono acetatas; Prednizolonu octan; Преднизолона Ацетат.

Prednisolone 21-acetate.

$C_{23}H_{30}O_6$=402.5

CAS — 52-21-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — 8B2807733D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Prednisolone Acetate). A white or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Prednisolone Acetate). A white to practically white, odourless, crystalline powder. Practically insoluble in water; soluble 1 in 120 of alcohol; slightly soluble in acetone and in chloroform. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Prednisolone Caproate *(rINNM)* ⊗

Caproato de prednisolona; Prednisolona, caproato de; Prednisolone, Caproate de; Prednisolone Hexanoate (BANM); Prednisoloni Caproas; Преднизолона Капроат.

Prednisolone 21-hexanoate.

$C_{27}H_{38}O_6$=458.6

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

Prednisolone Hydrogen Succinate

(BANM, rINNM) ⊗

Hidrogenosuccinato de prednisolona; Prednisolona, hidrogenosuccinato de; Prednisolone Hemisuccinate; Prednisolone, Hémisuccinate de; Prednisoloni Hemisuccinas; Преднизолона Гемисукцинат.

Prednisolone 21-(hydrogen succinate).

$C_{25}H_{32}O_8$=460.5

CAS — 2920-86-7.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — G7080T74ON.

Pharmacopoeias. In *Jpn* and *US.*

USP 36: (Prednisolone Hemisuccinate). A fine, creamy-white, practically odourless, powder with friable lumps. Soluble 1 in 4170 of water, 1 in 6.3 of alcohol, 1 in 1064 of chloroform, and 1 in 248 of ether; soluble in acetone. Store in airtight containers.

Prednisolone Metasulfobenzoate Sodium

(rINNM) ⊗

ATL-2502; Metasulfobenzoato sódico de prednisolona; Natrii Prednisoloni Metasulfobenzoas; Prednisolona, metasulfobenzoato sódico de; Prednisolone Métasulfobenzoate Sodique; Prednisolone Metasulphobenzoate Sodium (BANM); Prednisolone Sodium Metasulphobenzoate; Prednisolone Sodium Metazoate (USAN); R-812; Натрий Метасульфобензоат Преднизолон.

Prednisolone 21-(sodium *m*-sulphobenzoate).

$C_{28}H_{31}NaO_9S$=566.6

CAS — 630-67-1.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — D34STHM53T.

Prednisolone Pivalate *(BANM, rINNM)* ⊗

Pivalato de prednisolona; Prednisolona, pivalato de; Prednisolone, Pivalate de; Prednisolone Trimethylacetate; Prednisoloni Pivalas; Prednisolonipivalaatti; Prednisolonpivalat; Prednisolon-pivalát; Prednizolono pivalatas; Prednizolon-pivalát; Prednizolonu piwalan; Преднизолона Пивалат.

Prednisolone 21-pivalate.

$C_{26}H_{36}O_6$=444.6

CAS — 1107-99-9.

ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.

ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.

UNII — 24W6S37NXU.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Prednisolone Pivalate). A white, or almost white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. Protect from light.

Prednisolone Sodium Phosphate

(BANM, rINNM) ⊗

Fosfato sódico de prednisolona; Natrii Prednisoloni Phosphas; Prednisolona, fosfato sódico de; Prednisolondihydrogenphosphat-Dinatrium; Prednisolone, Phosphate Sodique de; Prednisolonfosfát sodná sůl; Prednisoloni Natrii Phosphas; Prednisoloninatriumfosfaatti; Prednisolonnatriumfosfat; Prednizolon Sodyum Fosfat; Prednizolonnátrium-foszfát; Prednizolono natrio fosfatas; Натрия Преднизолона Фосфат.

Prednisolone 21-(disodium orthophosphate).

$C_{21}H_{27}Na_2O_8P$=484.4

CAS — 125-02-0.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — M021NXA9L.

NOTE. **PRED** is a code approved by the BP 2014 for use on single unit doses of eye drops containing prednisolone sodium phosphate where the individual container may be too small to bear all the appropriate labelling information.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Prednisolone Sodium Phosphate). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Protect from light.

USP 36: (Prednisolone Sodium Phosphate). A white or slightly yellow friable granules or powder. Is odourless or has a slight odour. Is slightly hygroscopic. Soluble 1 in 4 of water and 1 in 13 of methyl alcohol; slightly soluble in alcohol and in chloroform; very slightly soluble in acetone and in dioxan. pH of a 1% solution in water is between 7.5 and 10.5. Store in airtight containers.

Prednisolone Sodium Succinate

(BANM, rINNM) ⊗

Prednisolona, succinato sódico de; Prednisolone Sodium Hemisuccinate; Prednisolone, Succinate Sodique de; Prednisoloni Natrii Succinas; Succinato sódico de prednisolona; Преднизолона Натрия Сукцинат.

11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione 21-(sodium succinate).

$C_{25}H_{31}NaO_8$=482.5

CAS — 1715-33-9.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — 8223RR9DWF.

Pharmacopoeias. *Jpn* and *US* include Prednisolone Sodium Succinate for Injection.

USP 36: (Prednisolone Sodium Succinate for Injection). A creamy white powder with friable lumps, having a slight odour.

Prednisolone Steaglate *(BAN, rINNM)* ⊗

Esteaglato de prednisolona; Prednisolona, esteaglato de; Prednisolone, Stéaglate de; Prednisoloni Steaglas; Преднизолона Стеаглат.

Prednisolone 21-stearoylglycolate.

$C_{41}H_{64}O_8$=685.0

CAS — 5060-55-9.
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — OZQ2XN817F.

Prednisolone Tebutate *(BANM, rINNM)* ⊗

Prednisolona, tebutato de; Prednisolone Butylacetate; Prednisolone, Tébutate de; Prednisolone 21-*tert*-Butylacetate; Prednisolone Tertiary-Butylacetate; Prednisoloni Tebutas; Tebutato de prednisolona; Преднизолона Тебутат.

Prednisolone 21-(3,3-dimethylbutyrate).

$C_{27}H_{36}O_6.H_2O$=476.6

CAS — 7681-14-3 (anhydrous prednisolone tebutate).
ATC — A07EA01; C05AA04; D07AA03; H02AB06; R01AD02; S01BA04; S02BA03; S03BA02.
ATC Vet — QA07EA01; QC05AA04; QD07AA03; QH02AB06; QR01AD02; QS01BA04; QS02BA03; QS03BA02.
UNII — JVZANU282K.

Pharmacopoeias. In *US*.

USP 36: (Prednisolone Tebutate). A white to slightly yellow, hygroscopic, free-flowing powder, which may show some soft lumps. Is odourless or has not more than a moderate characteristic odour. Very slightly soluble in water; sparingly soluble in alcohol and in methyl alcohol; soluble in acetone; freely soluble in chloroform and in dioxan. Store in airtight containers sealed under nitrogen at a temperature not exceeding 8 degrees.

Uses and Administration

Prednisolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1): 5 mg of prednisolone is equivalent in anti-inflammatory activity to about 25 mg of cortisone acetate. In general, prednisolone, either in the form of the free alcohol or in one of the esterified forms, is the drug of choice in the UK for conditions in which routine systemic corticosteroid therapy is indicated (see p. 1597.3), except adrenocortical-deficiency states for which hydrocortisone with supplementary fludrocortisone is preferred. The more potent pituitary-suppressant properties of a glucocorticoid such as dexamethasone may, however, be required for the diagnosis and management of conditions associated with adrenal hyperplasia.

The dose may be expressed in terms of the base, and the following are each equivalent to about 100 mg of prednisolone:

- prednisolone acetate 110 mg
- prednisolone caproate 127 mg
- prednisolone hydrogen succinate 128 mg
- prednisolone metasulfobenzoate sodium 157 mg
- prednisolone pivalate 123 mg
- prednisolone sodium phosphate 135 mg
- prednisolone sodium succinate 134 mg
- prednisolone steaglate 190 mg
- prednisolone tebutate 132 mg

However, esterification generally alters potency and compounds with equivalent prednisolone content may not have equivalent clinical effect.

When given **orally** prednisolone is usually used although the acetate, sodium phosphate, and steaglate are also given; the usual dose, expressed in terms of prednisolone, is about 2.5 to 60 mg daily in divided doses, as a single daily dose after breakfast, or as a double dose on alternate days. Alternate-day early-morning dosage regimens produce less suppression of the hypothalamic-pituitary axis but may not always provide adequate control. Enteric-coated tablets of prednisolone are also available (for the view that these should not be used in patients with inflammatory bowel disease, see below).

For **parenteral use** the sodium phosphate ester has been given either intravenously by injection or infusion, or intramuscularly by injection. An aqueous suspension of prednisolone acetate is also used intramuscularly for a prolonged effect, in doses of 25 to 100 mg once or twice weekly. The sodium succinate ester has also been given parenterally.

For **intra-articular injection** suggested doses are 5 to 25 mg of prednisolone acetate. The sodium phosphate and tebutate esters have been given by intra-articular injection, intralesional injection, and by injection into soft tissue.

Prednisolone acetate and prednisolone sodium phosphate are also used in the **topical treatment** of allergic and inflammatory conditions of the eyes or ears, usually as drops containing 0.5 or 1%. Prednisolone has also been used topically as the free alcohol and as the hemisuccinate, pivalate, metasulfobenzoate sodium, and sodium acetate esters.

For **rectal use** prednisolone metasulfobenzoate sodium or prednisolone sodium phosphate are often given. Retention enemas containing the equivalent of 20 mg of prednisolone per 100 mL, rectal foam containing the equivalent of 20 mg of prednisolone per dose, or suppositories containing the equivalent of 5 mg of prednisolone are available. Prednisolone has also been used rectally as the free alcohol and as the acetate and caproate esters.

Other esters of prednisolone that have occasionally been used include the farnesil, palmitate, sodium tetrahydrophthalate, and valeroacetate.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively).

Owing to its less pronounced mineralocorticoid activity prednisolone is less likely than cortisone or hydrocortisone to cause sodium retention, electrolyte imbalance, and oedema. Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Breast feeding. Concentrations of prednisone and prednisolone in breast milk from a woman 120 minutes after prednisone 10 mg orally were found to be 26.7 nanograms and 1.6 nanograms/mL respectively.[1] In another 7 women given a single 5-mg oral dose of tritium-labelled prednisolone, a mean of 0.14% of the radioactivity from the dose was recovered per litre of milk in the next 48 to 61 hours.[2] In a study of 3 women, only about 0.025% of a single intravenous dose of prednisolone phosphate 50 mg was found in breast milk over 6 hours.[3] During maintenance therapy with prednisolone in daily doses of 10 to 80 mg in 6 women, the milk to serum concentration ratio of prednisolone ranged from 0.2, for doses of 30 mg or more, to 0.1 for lower doses.[4] The authors estimated that a breast-fed infant would receive less than 0.1% of the maternal dose of prednisolone, and that this would be a negligible addition to the infant's endogenous cortisol production. They also concluded that exposure could be minimised by breast feeding at least 4 hours after the dose.

A review[5] by the UK CSM remarked that prednisolone was distributed into breast milk in small amounts and recommended that infants of mothers receiving 40 mg or more daily should be monitored for signs of adrenal suppression. The American Academy of Pediatrics considers[6] that the use of prednisone or prednisolone is usually compatible with breast feeding.

1. Katz FH, Duncan BE. Entry of prednisone into human milk. *N Engl J Med* 1975; 293: 1154.
2. McKenzie SA, *et al.* Secretion of prednisolone into breast milk. *Arch Dis Child* 1975; 50: 894–6.
3. Greenberger PA, *et al.* Pharmacokinetics of prednisolone transfer to breast milk. *Clin Pharmacol Ther* 1993; 53: 324–8.
4. Öst L, *et al.* Prednisolone excretion in human milk. *J Pediatr* 1985; 106: 1008–11.
5. CSM/MCA. Systemic corticosteroids in pregnancy and lactation. *Current Problems* 1998; 24: 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023926&RevisionSelectionMethod=LatestReleased (accessed 20/06/06)
6. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/04/04)

Hepatic impairment. Conversion of prednisone to prednisolone has been reported to be impaired in chronic active liver disease.[1,2] However, although plasma-prednisolone concentrations were found to be more predictable after prednisolone than prednisone in a group of healthy subjects,[3] no difference was noted in patients with chronic active hepatitis, in whom impaired elimination of prednisolone compensated for any impaired conversion of prednisone. A review of the pharmacokinetics of prednisone and prednisolone[4] concluded that fear of inadequate conversion of prednisone into prednisolone was not justified.

1. Powell LW, Axelsen E. Corticosteroids in liver disease: studies on the biological conversion of prednisone to prednisolone and plasma protein binding. *Gut* 1972; 13: 690–6.
2. Madsbad S, *et al.* Impaired conversion of prednisone to prednisolone in patients with liver cirrhosis. *Gut* 1980; 21: 52–6.
3. Davis M, *et al.* Prednisone or prednisolone for the treatment of chronic active hepatitis? A comparison of plasma availability. *Br J Clin Pharmacol* 1978; 5: 501–5.
4. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; 19: 126–46.

Inflammatory bowel disease. Symptoms recurred in a patient with Crohn's disease on changing from conventional to enteric-coated tablets of prednisolone.[1] This was not an isolated occurrence in the authors' unit, and it was advocated that only non-enteric-coated prednisolone tablets should be used in Crohn's disease, and that the enteric-coated form be used with caution in any condition characterised by diarrhoea or a rapid transit time.

1. Beattie RM, Walker-Smith JA. Use of enteric coated prednisolone in Crohn's disease. *Arch Dis Child* 1994; 71: 282.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednisolone, when given by most routes, as probably not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed. However, NAPOS also suggests that prednisolone rectal ointment and suppositories are possibly porphyrinogenic and as such it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 07/11/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Prednisolone and prednisone are both readily absorbed from the gastrointestinal tract, but whereas prednisolone already exists in a metabolically active form, prednisone must be converted in the liver to its active metabolite, prednisolone. In general, this conversion is rapid so this difference is of little consequence when seen in the light of intersubject variation in the pharmacokinetics of prednisolone itself; bioavailability also depends on the dissolution rates of the tablet formulations. As discussed under Hepatic Impairment, above, reduced corticosteroid concentrations when giving prednisone to patients with liver disease do not seem to be a problem in practice. After intramuscular doses the sodium phosphate ester of prednisolone is rapidly absorbed whereas the acetate, in the suspension form, is only slowly absorbed.

Peak plasma concentrations of prednisolone occur 1 or 2 hours after an oral dose, and it has a usual plasma half-life of 2 to 4 hours. Its initial absorption, but not its overall bioavailability, is affected by food.

Prednisolone is extensively bound to plasma proteins, although less so than hydrocortisone (cortisol). The volume of distribution, and also the clearance are reported to increase with an increase from low to moderate doses; at very high doses, clearance appears to become saturated.

Prednisolone is excreted in the urine as free and conjugated metabolites, with an appreciable proportion of unchanged prednisolone. Prednisolone is largely inactivated as it crosses the placenta; small amounts are excreted in breast milk.

Prednisolone has a biological half-life lasting several hours, intermediate between those of hydrocortisone (cortisol) and the longer-acting glucocorticoids, such as dexamethasone. It is this intermediate duration of action that makes it suitable for the alternate-day dosage regimens which have been found to reduce the risk of adrenocortical insufficiency, yet provide adequate corticosteroid coverage in some disorders.

General reviews of the pharmacokinetics of prednisolone[1,2] and some references to its pharmacokinetics in healthy subjects[3] and in various disease states.[4–8]

1. Begg EJ, *et al.* The pharmacokinetics of corticosteroid agents. *Med J Aust* 1987; 146: 37–41.
2. Frey BM, Frey FJ. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1990; 19: 126–46.
3. Rohatagi S, *et al.* Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997; 37: 916–25.
4. Berghouse LM, *et al.* Plasma prednisolone levels during intravenous therapy in acute colitis. *Gut* 1982; 23: 980–3.
5. Shaffer JA, *et al.* Absorption of prednisolone in patients with Crohn's disease. *Gut* 1983; 24: 182–6.
6. Reece PA, *et al.* Prednisolone protein binding in renal transplant patients. *Br J Clin Pharmacol* 1985; 20: 159–62.
7. Frey FJ, *et al.* Altered metabolism and decreased efficacy of prednisolone and prednisone in patients with hyperthyroidism. *Clin Pharmacol Ther* 1988; 44: 510–21.
8. Miller PFW, *et al.* Pharmacokinetics of prednisolone in children with nephrosis. *Arch Dis Child* 1990; 65: 196–200.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Cortizul†; Ultracortenol; *Austral.*: Panafcortelone; Predmix; Predsol; Predsolone; Redipred; Solone; Sterofrin†; *Austria*: Aprednislon; Kuhlpred-non; Rectopred; Solu-Dacortin; Ultracortenol; *Belg.*: Pred Forte; Ultracortenol†; *Braz.*: Oftpred; Oralpred; Pred Fort; Pred Mild; Predsim; Prelone; Ster; *Canad.*: Diopred; Pediapred; Pred Forte; Pred Mild; *Chile*: Pred Forte; Predsolets; Sophipren; *China*: Pred Forte (百力特); *Cz.*: Linola-H-Fett N†; Predni-POS; Ultracortenol; *Denm.*: Pred-Clysma; Ultracortenol; *Fin.*: Di-Adreson-F; Pred Forte; Ultracortenol; *Fr.*: Hydrocortancyl; Solupred; *Ger.*: Decortin H; Dermosolon; Dontisolon D; hefasolon; Infectocortikrupp; Inflanefran; Klismacort; Linola-H N; Linola-H-Fett N; Lygal Kopftinktur N; Predni H; Predni-Ophtal; Predni-POS; Predni; Prednigalen; Prednihexal†; Prednisolut; Solu-Decortin H; Ultracortenol; *Gr.*: Adelcort; Adelone; Deltacortril; Prezolon; Solupred; *Hong Kong*: Delcorlon†; Desolon†; Dhasolone; Di-Adreson-F†; Panafcortelone; Pred Forte; Pred Mild; Predenema†; Predfoam; Redipred; Ultracortenol†; Xepasone†; *Hung.*: Di-Adreson-F†; Linola-H N†; Linola-H-Fett N†; Ultracortenol†; *India*: Acticort; Anesolin; Aquapred; Delsone; Deltacortril; Dispred DPS; Elpred; Emsolone; GB-Pred AC; Hostacortin H; Immupress; Kidpred; Nisolone; Nucort-P; Nucort; Omnacortil; Predone; Wysolone; *Irl.*: Deltacortril; Pred Forte; Pred Mild; Predenema†; Predfoam†; Prednesol; Predsol; *Israel*: Danalone; Pred Forte; Ultracortenol†; *Ital.*: Deltacortenesol; *Jpn*: Parnerate†; Farnezone; Lidomex; Livimex; Predonema; *Malaysia*: Dhasolone; Econopred; Nisolon; Pred Forte; Pred Mild; Predon; Zoralone; *Mex.*: Cetapred; Delta Corti; Delta-Diona; Desnisol; Fisopred; Meticortelone; Pred-NF; Pred; Prednefrin SF; Sophipren; *Neth.*: Di-Adreson-F; Pred Forte; Ultracortenol; *Norw.*: Pred-Clysma; Ultracortenol; *NZ*: Pred Forte; Pred Mild; Redipred; *Philipp.*: Histacort; Ilocet; Inflastat; Ipredniz; Isolone; Liquipred; Liquisone; Medsone; Optipred; Pred Forte; Predisyr; Prednecort; Romamed; Syrupred†; Vistapred; *Pol.*: Encortolon; Fenicort; Mecortolon; *Port.*: Frisolona; Lepicortinolo; Predniocil; Solu-Dacortina; *Rus.*: Medopred (Медопред); *S.Afr.*: Aspelone; Capsoid; Lenisolone; Pred Forte; Pred Mild; Preflam; Prelone; *Singapore*: Delcorlon; Deltasolone; Dhasolone; Econopred; Pred; Prelone-3; SP-Cortil; Walesolone; Xepasone; *Spain*: Estilsona; Pred Forte; *Swed.*: Precortalon aquosum; Pred-Clysma; Ultracortenol; *Switz.*: Hexacortone; Pred Forte; Premandol; Spiricort; Ultracortenol; *Thai.*: Clinipred; Di-Adreson-F; Fortisone; Inf-Oph; Neosolone; Opredsone; Polypred; Pred Forte; Pred Mild; Predcap; Predi; Predisole; Predman; Prednersone; Prednisil†; Predsomed; Presoga; *Turk.*: Codelsol†; Codelton†; Deltacortril; Hexacorton; Neocorten; Norsol; Pred Forte; Predni-POS; Prednol; Prozolon; *UAE*: Gupisone; *UK*: Deltacortril; Deltastab; Precortisyl; Pred Forte; Predenema†; Predfoam†; Predsol; *USA*: AsmalPred Plus; Flo-Pred; Key-Pred-SP; Millipred; Omnipred; Orapred; Pediapred; Pred Forte; Pred Mild; Pred-Phosphate; Pred; Predcor; Prednisol†; Prelone; Veripred; *Venez.*: Meticortelone; Ocupred; Sintisone; Sophipren.

Multi-ingredient Preparations. *Arg.*: Afluhist Plus; Bactio Rhin Prednisolona; Blefamide; Cortizul†; Delta Tomanil B12; Deltar; Efecoryl Forte; Esodar; Fenipred; Neocortizul†; Oftaldrop; Otidrops; Prednefrin; Prednifarma; Prednifarma; Procto Venart; Relefrina†; Rucaten Prednisolona; Scheriproct; Solupred†; *Austral.*: Prednefrin; Scheriproct; *Austria*: Delta-Hadensa; Scheriproct; *Belg.*: Hemosedan; Predmycin P; Scheriproct; Sofrasolone; *Braz.*: Colutoide; Fonergin; Isopto Cetapred; Polipred; Predmicin; Rifocort; Rinisone; Zypred; *Canad.*: Ak-Cide; Blephamide; Dioptimyd; *Chile*: Banedif Oftalmico con Prednisolona†; Blefamide†; Blefamide; Deltamid; Gemitin con Prednisolona; Scheriproct; Sintoftona; *China*: Poly Pred (帕利百); *Cz.*: Alpicort F; Alpicort; Imacort; *Fin.*: Scheriproct; *Fr.*: Cortisal; Deliproct; Derinox; Deturgylone; *Ger.*: Alpicort P; Alpicort; Aquapred†; Bismolan H Corti; Blephamide; Imazol comp; *Inflanegent*; Leioderm P; Linoladiol-H N; *Gr.*: Blephamide; Blikosan; Dermol; Hemorrocort; Isopto Cetapred; Precortivit; Scheriproct Neo; *Hong Kong*: Pilelife†; *Hung.*: Alpicort F; Alpicort; Aurobin; Prednisolon J†; Rheosolon; *India*: Atrisolon; Chloramsone; Exopred; Ocepred; Ofelder-PA; Oflacin-P; Perfocyn†; *Indon.*: Borraginol-S; Chloramphecort-H; Klorfeson; *Irl.*: Predmycin-P; Scheriproct; *Israel*: Allumycin; Blephamide; Threolone; *Ital.*: Bio-Delta Cortilen; Deltamidrina; Solprene; *Mex.*: Artrilan†; Blefamide-F; Blefamide; Dartrizon; Deltamid; Deltron; Isopto Cetapred; Obrypre; Otalgan; Premid; Scheriproct; *Norw.*: Scheriproct; *NZ*: Blephamide†; *Philipp.*: Cetapred†; Exopred; Histacort; Isopto Cetapred†; Lonace; Predmycin-P; Sterilid-V; *Pol.*: Alpicort E; Alpicort; Mecortolon N; *Port.*: Anacal; Conjunctilone-S; Meocil; Neo-Davisolona; Prednifalmina; Scheriproct; *Rus.*: Aurobin (Ауробин); Dermosolon (Дермозолон); Gyterna (Гитерна); Hepatrombin H (Гепатромбин Г); Hepazolon (Гепазолон); Insanovin (Инсановин); Tergynan (Тержинан); *S.Afr.*: Scheriproct; *Singapore*: Blephamide†; Predmycin-P†; *Spain*: Alergical; Antigrietun; Kanapomada†; Nasopomada†; Poly Pred; Rinobanedif; Rinovel†; Ruscus; Teolixir Compositum†; *Swed.*: Scheriproct N; *Switz.*: Alpicort F; Blephamide; Imacort; Locaseptil-Neo; Mycinopred†; Scheriproct; *Thai.*: Denson†; Exopred; Farakil; Levoptin; Mysolone-N; Neozolone; Pred Oph; Predmycin P; Prednisil-N†; Prednisolone-N; Unipred; *Turk.*: Blephamide; Kortisetin; Otimisin; Prednol-A; Suprenil; *UK*: Predsol-N†; Scheriproct; *Ukr.*: Aurobin (Ауробин); Dermosolon (Дермозолон)†; Hepathrombin H (Гепатромбин Г); Imacort (Имакорт); Neotrizol (Неотризол); Prednicarb (Предникарб); Tergynan (Тержинан); *USA*: Blephamide; Metimyd†; Poly-Pred†; Pred G; Sulfamide; Vasocidin; Vasocine; *Venez.*: Clorasona; Permucal; Scheriproct; Sulfacort.

Homoeopathic Preparations. *Ger.*: NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†.

Pharmacopoeial Preparations

BP 2014: Gastro-resistant Prednisolone Tablets; Prednisolone Acetate Injection; Prednisolone Enema; Prednisolone Sodium Phosphate Ear Drops; Prednisolone Sodium Phosphate Eye Drops; Prednisolone Tablets;

USP 36: Chloramphenicol and Prednisolone Ophthalmic Ointment; Gentamicin and Prednisolone Acetate Ophthalmic Ointment; Neomycin and Polymyxin B Sulfates and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Acetate Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Ointment; Neomycin Sulfate and Prednisolone Acetate Ophthalmic Suspension; Neomycin Sulfate and Prednisolone Sodium Phosphate Ophthalmic Ointment; Neomycin Sulfate, Sulfacetamide Sodium, and Prednisolone Acetate Ophthalmic Ointment; Prednisolone Acetate Injectable Suspension; Prednisolone Acetate Ophthalmic Suspension; Prednisolone Cream; Prednisolone Sodium Phosphate Injection; Prednisolone Sodium Phosphate Ophthalmic Solution; Prednisolone Sodium Succinate for Injection; Prednisolone Syrup; Prednisolone Tablets; Prednisolone Tebutate Injectable Suspension; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Ointment; Sulfacetamide Sodium and Prednisolone Acetate Ophthalmic Suspension.

Prednisone *(BAN, rINN)* ⊗

1,2-Dehydrocortisone; Deltacortisone; Deltadehydrocortisone; Metacortandracin; NSC-10023; Prednison; Prednisona; Prednisoni; Prednisonum; Prednizon; Prednizonas; Преднизон.

17α,21-Dihydroxypregna-1,4-diene-3,11,20-trione.

$C_{21}H_{26}O_5$=358.4

CAS — 53-03-2.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

UNII — V80R961HZT.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows the anhydrous form or the monohydrate.

Ph. Eur. 8: (Prednisone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

USP 36: (Prednisone). It contains one molecule of water of hydration or is anhydrous. A white to practically white, odourless, crystalline powder. Very slightly soluble in water; soluble 1 in 150 of alcohol and 1 in 200 of chloroform; slightly soluble in dioxan and in methyl alcohol.

Prednisone Acetate *(BANM, rINNM)* ⊗

Acetato de prednisona; Prednisona, acetato de; Prednisone, Acétate de; Prednisoni Acetas; Prednizonu octan; Преднизона Ацетат.

Prednisone 21-acetate.

$C_{23}H_{28}O_6$=400.5.

CAS — 125-10-0.

ATC — A07EA03; H02AB07.

ATC Vet — QA07EA03; QH02AB07.

UNII — OU93QEL83U.

Pharmacopoeias. In *Chin.* and *Pol.*

Profile

Prednisone is a biologically inert corticosteroid that is converted in the liver to the mainly glucocorticoid corticosteroid prednisolone. It has the same chemical relationship to prednisolone as cortisone has to hydrocortisone. The indications and dosage of prednisone for oral use are exactly the same as those for prednisolone (see p. 1646.1, and the chapter introduction, p. 1597.3).

In the UK prednisolone has historically been preferred to prednisone, on the grounds that it does not require conversion to the active substance, but in practice this is rarely significant (see Hepatic Impairment, under Prednisolone, p. 1646.3), and in some countries, such as the USA, prednisone is the drug of choice for many of the conditions in which routine systemic corticosteroid therapy is indicated.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies prednisone as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Meticorten; Metilpres; Prednipirine; *Austral.*: Panafcort; Predsone; Sone; *Austria*: Lodotra; *Belg.*: Lodotra; *Braz.*: Artinizona; Becortem; Corticorten; Flamacorten; Meticorten; Precortil; Predison†; Prednax; Prednis; Predson; Predval; *Canad.*: Winpred; *Chile*: Bersen; Cortiprex; Meticorten; Procion; *Cz.*: Rectodelt; *Denm.*: Lodotra; *Fin.*: Lodotra; *Fr.*: Cortancyl; *Ger.*: Decortin; Lodotra; Predni Tablinen; Rectodelt; *Gr.*: Chrocort; *Hung.*: Rectodelt; *Indon.*: Inflason; Nufapredson; Pehacort; *Israel*: Lodotra; *Ital.*: Deltacortene; Lodotra; *Mex.*: Artrinol-On; Ednapron†; Losinon; Meprosona-F; Meticorten; Norapred; Prednidib; *Neth.*: Lodotra; *Norw.*: Lodotra; *Philipp.*: Biosone; Bioster†; Endosone; Oracort†; Orasone; Pred; Predoral; Predsone; Prolix; Qualisone; Steerometz†; *Pol.*: Encorton; Lodotra; *Port.*: Lodotra; Meticorten; Nocaslo†; *S.Afr.*: Meticorten; Panafcort; Predelitin†; Pulmison; Trolic; *Spain*: Dacortin; *Swed.*: Deltison; Lodotra; *Switz.*: Lodotra; *UK*: Lodotra; *Ukr.*: Rectodelt (Ректодельт); *USA*: Deltasone; Liquid Pred; Meticorten; Panasol-S; Rayos; Sterapred†; *Venez.*: Meticorten.

Multi-ingredient Preparations. *Arg.*: Peganix; *Austria*: Fluorex Plus; Oleomycetin-Prednison†; *Chile*: Alerzona†; *Mex.*: Barigesic†; Pre Clor; *Spain*: Colliriocilina Prednisona†; Flacin†; Kanafosal Predni†; Prednisona Neomicina.

Pharmacopoeial Preparations

USP 36: Prednisone Oral Solution; Prednisone Tablets.

Rimexolone *(BAN, USAN, rINN)* ⊗

Org-6216; Rimeksolon; Rimeksolonі; Rimexolon; Rimexolona; Rimexolonum; Trimexolone; Римексолон.

11β-Hydroxy-16α,17α-dimethyl-17β-propionylandrosta-1,4-dien-3-one.

$C_{24}H_{34}O_3$=370.5

CAS — 49697-38-3.

ATC — H02AB12; S01BA13.

ATC Vet — QH02AB12; QS01BA13.

UNII — O7M2E4264D.

Pharmacopoeias. In *US.*

USP 36: (Rimexolone). A white to off-white powder. Freely soluble in chloroform; sparingly soluble in methyl alcohol.

Profile

Rimexolone is a corticosteroid applied topically to the eye for its glucocorticoid activity (see p. 1597.1) in the treatment of inflammatory eye disorders including uveitis (p. 1615.1) and postoperative inflammation. It is used as a 1% suspension.

Prolonged use of ophthalmic preparations containing corticosteroids has caused raised intra-ocular pressure and reduced visual function.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies rimexolone as not

porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Vexol; ***Belg.***: Vexolon; ***Braz.***: Vexol; ***Canad.***: Vexol; ***Denm.***: Vexol; ***Fin.***: Vexol; ***Fr.***: Vexol; ***Ger.***: Vexol; ***Gr.***: Vexol; ***Hong Kong***: Vexol; ***Irl.***: Vexol; ***Ital.***: Vexol; ***Mex.***: Vexol; ***Neth.***: Vexol; ***Norw.***: Vexol; ***NZ***: Vexol; ***Port.***: Vexol; ***Singapore***: Vexol; ***Spain***: Vexol; ***Swed.***: Vexol; ***Switz.***: Vexol; ***Turk.***: Vexol; ***UK***: Vexol; ***USA***: Vexol.

Pharmacopoeial Preparations
USP 36: Rimexolone Ophthalmic Suspension.

Suprarenal Cortex ⊗

Corteza suprarrenal.

Profile

Suprarenal cortex contains a number of steroid compounds the most active of which are corticosterone, dehydrocorticosterone, hydrocortisone, cortisone, and aldosterone. It has been prepared from the adrenal glands of oxen. Suprarenal cortex was formerly used intramuscularly for the treatment of adrenocortical insufficiency but it has been superseded by hydrocortisone and other corticosteroids (see p. 1600.2).

Suprarenal cortex is an ingredient of a wide range of preparations, often with other organ extracts or vitamins, promoted for indications ranging from asthenia to liver disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austria***: Mobilat; ***Belg.***: Mobilat; ***Braz.***: Mobilat; ***Chile***: Mobilat†; Cz.: Mobilat; ***Fin.***: Mobilat; ***Philipp.***: Mobilat; ***Pol.***: Mobilat; ***Thai.***: Mobilat.

Homoeopathic Preparations. ***Neth.***: Chavita 2; Emvita 6; Emvita 7.

Tetracosactide *(BAN, rINN)* ⊗

Cosintropina; Cosyntropin (USAN); Tetracosactid; Tetracosactida; Tétracosactide; Tetracosactido; Tetracosactidum; Tetracosactrin; Tetracosactrina; Tetrakosaktid; Tetrakosaktidi; Tetrakosaktrin; Tetrakozaktidas; Тетракозактид.

Corticotrophin-(1–24)-tetracosapeptide; Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-Lys-Val-Tyr-Pro.

$C_{136}H_{210}N_{40}O_{31}S$=2933.5

CAS — 16960-16-0 (tetracosactide); 22633-88-1 (tetracosactide hexa-acetate); 60189-34-6 (tetracosactide x acetate).

ATC — H01AA02.

ATC Vet — QH01AA02.

UNII — 72YY86EA29.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tetracosactide). A synthetic tetracosapeptide in which the sequence of amino acids is the same as that of the first 24 residues of human corticotropin. It is available as an acetate. It increases the rate at which corticoid hormones are secreted by the adrenal gland. By convention, 1 microgram of tetracosactide is equivalent to 1 unit of tetracosactide. A white or yellow, amorphous powder. Sparingly soluble in water. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Uses and Administration

Tetracosactide is a synthetic polypeptide with general properties similar to those of corticotropin (p. 1628.3). Tetracosactide is used diagnostically to investigate adrenocortical insufficiency (p. 1600.2).

Although tetracosactide, like corticotropin, has also been used therapeutically for most of the conditions in which systemic corticosteroid therapy is indicated, it is now rarely used for such indications.

Tetracosactide is usually used in the form of the acetate although doses are often expressed in terms of tetracosactide itself.

For *diagnostic purposes* tetracosactide acetate is used intramuscularly or intravenously as a plain injection in the first instance then, if results are inconclusive, intramuscularly as a long-acting depot injection. The initial test using the plain injection is based on the measurement of plasma-cortisol concentrations immediately before and exactly 30 minutes after an intramuscular or intravenous injection equivalent to 250 micrograms of tetracosactide; adrenocortical function may be regarded as normal if there is a rise in the cortisol concentration of at least 200 nanomoles/litre (70 micrograms/litre). In some cases the dose may be given by intravenous infusion over 6 hours to provide a greater stimulus of the adrenal glands, with cortisol concentrations measured before and at the end of the infusion. A low-dose test using 1 microgram has also been used (see Diagnostic Use, below).

If the results of this test are equivocal, or where functional reserve of the adrenal cortex is to be determined, the long-acting depot preparation may be used, the dose being 1 mg of tetracosactide acetate given intramuscularly. Adrenocortical function is regarded as normal if plasma-cortisol concentrations have steadily increased to 1000 to 1800 nanomoles/litre 5 hours after the injection. A 3-day test, for example with 1 mg of the depot preparation given each morning, is also used to differentiate between primary and secondary adrenocortical insufficiency; this is preceded on the first day and followed on the fourth day by the test using the plain injection. A marked improvement in the second assessment suggests secondary adrenocortical insufficiency.

For *therapeutic purposes* tetracosactide acetate has been given by intramuscular injection as the long-acting depot preparation. The usual initial dose of tetracosactide acetate has been 1 mg daily (or 1 mg every 12 hours in acute cases), reduced after the acute symptoms have been controlled to 0.5 to 1 mg every 2 or 3 days or 1 mg weekly.

For doses used in children, see below.

Administration in children. For diagnostic use, children may be given an intravenous or intramuscular dose of the plain injection of tetracosactide 145 micrograms/m², to a maximum of 250 micrograms. The *BNFC* also includes a low-dose test of 300 nanograms/m².

Tetracosactide acetate in a long-acting depot preparation has been given intramuscularly for therapeutic use in conditions requiring systemic corticosteroid therapy. For children aged 3 to 5 years old, an initial dose of 250 to 500 micrograms has been given daily, and then every 2 to 8 days for maintenance. A dose of 0.25 to 1 mg has been used similarly in children aged 5 to 12 years.

Tetracosactide has also been used to manage infantile spasms (see Epilepsy, p. 506.1). For children aged 1 month and older, the *BNFC* suggests using the depot preparation in a dose of 500 micrograms by intramuscular injection, given on alternate days and adjusted according to response.

Diagnostic use. Tetracosactide is widely used in the diagnosis of adrenal insufficiency (p. 1600.2). It is usually given by intramuscular or intravenous injection in a dose of 250 micrograms, with plasma-cortisol concentrations measured before and 30 minutes after the injection. The sensitivity of this test has been questioned, as such a high dose may produce a cortisol response in patients with partial adrenal gland atrophy, resulting in a missed diagnosis of secondary adrenal insufficiency. A low-dose test using an intravenous dose of 1 microgram has been proposed as a more sensitive test.

A meta-analysis[1] concluded that high- and low-dose tests performed similarly in the diagnosis of secondary adrenal insufficiency. However, the high-dose test was favoured because of the lack of a commercially available low-dose preparation. A later review[2] advocated the use of the low-dose test for diagnosing secondary insufficiency, but recommended the high-dose test for diagnosis of suspected primary adrenal insufficiency. Both considered that more study was needed of the use of these tests in critically ill patients.[1,2]

1. Dorin RI, *et al.* Diagnosis of adrenal insufficiency. *Ann Intern Med* 2003; 139: 194–204.
2. Magnotti M, Shimshi M. Diagnosing adrenal insufficiency: which test is best—the 1-microgram or the 250-microgram cosyntropin stimulation test? *Endocr Pract* 2008; 14: 233–8.

Post-dural puncture headache. There are anecdotal reports of the relief of post-dural puncture headache by corticotropin or, more recently, tetracosactide.[1-5] Intramuscular injection and intravenous infusion have both been used, but a controlled study[6] in 18 women found that a single intramuscular dose of tetracosactide 1 mg was no more beneficial than sodium chloride 0.9%. As discussed on p. 1979.1, many patients respond to conservative measures.

1. Collier BB. Treatment for post dural puncture headache. *Br J Anaesth* 1994; 72: 366–7.
2. Foster P. ACTH treatment for post-lumbar puncture headache. *Br J Anaesth* 1994; 73: 429.
3. Kshatri AM, Foster PA. Adrenocorticotropic hormone infusion as a novel treatment for postdural puncture headache. *Reg Anesth* 1997; 22: 432–4.
4. Carter BL, Pasupuleti R. Use of intravenous cosyntropin in the treatment of postdural puncture headache. *Anesthesiology* 2000; 92: 272–4.
5. Cánovas L, *et al.* Use of intravenous tetracosactin in the treatment of postdural puncture headache: our experience in forty cases. *Anesth Analg* 2002; 94: 1369.
6. Rucklidge MWM, *et al.* Synacthen Depot for the treatment of postdural puncture headache. *Anaesthesia* 2004; 59: 138–41.

Adverse Effects, Withdrawal, and Precautions

As for Corticotropin, p. 1629.1. Although hypersensitivity reactions, including anaphylaxis, may occur with the use of tetracosactide, it is reported to be less immunogenic than corticotropin; US licensed product information suggests that patients with a history of hypersensitivity to corticotropin may tolerate tetracosactide. In the UK, however, previous hypersensitivity to corticotropin or to tetracosactide is considered a contra-indication to tetracosactide use. Tetracosactide is also contra-indicated in patients with a history of allergic disorders such as asthma.

Since hypersensitivity reactions may occur up to 1 hour after injection, sufficient time should be allowed for recovery after use at the hospital or surgery. Self-administration is not recommended.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tetracosactide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

As for Corticosteroids, p. 1619.3.

Pharmacokinetics

On intravenous injection tetracosactide has triphasic pharmacokinetics. It is rapidly eliminated from plasma, mostly by distribution to the adrenal glands and kidneys. It is metabolised by serum endopeptidases into inactive oligopeptides, and then by aminopeptidases into free amino acids. Most of a dose is excreted in urine within 24 hours. The terminal half-life of tetracosactide is about 3 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Synacthen; ***Austria***: Synacthen; ***Belg.***: Synacthen; ***Canad.***: Cortrosyn; Synacthen Depot; ***Chile***: Synacthen; ***Denm.***: Synacthen; ***Fr.***: Synacthen; ***Ger.***: Synacthen Depot; Synacthen; ***Gr.***: Cortrosyn; Nuvacthe; Synacthene; ***Hong Kong***: Cortrosyn†; ***Irl.***: Synacthen; ***Israel***: Synacthen; ***Ital.***: Synacthen; ***Neth.***: Synacthen; ***NZ***: Synacthe; ***Port.***: Synacthen; ***Rus.***: Synacthen (Синактен)†; Synacthe Depot (Синактен Депо); ***S.Afr.***: Synacthen Depot; ***Spain***: Nuvacthen Depot; ***Swed.***: Synacthen; ***Switz.***: Synacthen Depo; Synacthen; ***Thai.***: Cortrosyn; ***Turk.***: Synacthen Depot; ***UK***: Synacthen Depot; Synacthen; ***USA***: Cortrosyn; ***Venez***: Synacthen.

Pharmacopoeial Preparations
BP 2014: Tetracosactide Injection; Tetracosactide Zinc Injection.

Tixocortol Pivalate *(BANM, USAN, rINNM)* ⊗

JO-1016; Pivalato de tixocortol; Tixocortol, Pivalate de Tixocortol, pivalato de; Tixocortoli Pivalas; Тиксокортола Пивалат.

11β,17α-Dihydroxy-21-mercaptopregn-4-ene-3,20-dione 21-pivalate.

$C_{26}H_{38}O_5S$=462.6

CAS — 61951-99-3 (tixocortol); 55560-96-8 (tixocortol pivalate).

ATC — A07EA05; R01AD07.

ATC Vet — QA07EA05; QR01AD07.

UNII — 6K28E35M3B.

Profile

Tixocortol pivalate is a corticosteroid with mainly glucocorticoid activity (p. 1597.1). It is used as buccal, nasal, throat, and rectal preparations. It is reported to undergo rapid first-pass metabolism, primarily in the liver, and to have minimal systemic effect.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fr.***: Pivalone; ***Singapore***: Pivalone; ***Switz.***: Pivalone†.

Multi-ingredient Preparations. ***Fr.***: Thiovalone; ***Switz.***: Pivalone compositum.

Triamcinolone *(BAN, rINN)* ⊗

9α-Fluoro-16α-hydroxyprednisolone; Fluoxiprednisolonum; Triamcinolon; Triamcinolona; Triamcinolonas; Triamcinolonum; Triamcynolon; Triamsinoloni; Триамцинолон.

9α-Fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione.
$C_{21}H_{27}FO_6$=394.4
CAS — 124-94-7.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QD07XB02; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — 1ZK20VI6TY.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Triamcinolone). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water and in dichloromethane; slightly soluble in methyl alcohol. Protect from light.

USP 36: (Triamcinolone). A white or practically white, odourless, crystalline powder. Very slightly soluble in water, in chloroform, and in ether; slightly soluble in alcohol and in methyl alcohol.

Triamcinolone Acetonide *(BANM, rINNM)* ⊗

Acetónido de triamcinolona; Triamcinolon acetonid; Triamcinolona, acetónido de; Triamcinolonacetonid; Triamcinolone, Acétonide de; Triamcinoloni acetonidum; Triamcinolono acetonidas; Triamcynolonu acetonid; Triamsinolon Asetonid; Triamsinoloniasetonidi; Триамцинолона Ацетонид.
9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione.
$C_{24}H_{31}FO_6$=434.5
CAS — 76-25-5.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — F446C597KA.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Chin. also includes Triamcinolone Acetonide Acetate.

Ph. Eur. 8: (Triamcinolone Acetonide). A white or almost white, crystalline powder. It shows polymorphism. Practically insoluble in water; sparingly soluble in alcohol. Protect from light.

USP 36: (Triamcinolone Acetonide). A white to cream-coloured crystalline powder, having not more than a slight odour. Practically insoluble in water; sparingly soluble in dehydrated alcohol, in chloroform, and in methyl alcohol. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Triamcinolone Acetonide Sodium Phosphate *(BANM, USAN, rINNM)* ⊗

CL-61965; CL-106359; Fosfato de sodio del acetónido de triamcinolona; Triamcinolona, acetónido de, fosfato de sodio del; Triamcinolone Acétonide, Phosphate Sodique de; Triamcinoloni Acetonidi Natrici Phosphas; Триамцинолона Ацетонида Натрия Фосфат.
Triamcinolone acetonide 21-disodium phosphate.
$C_{24}H_{30}FNa_2O_9P$=558.4
CAS — 1997-15-5.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.

Triamcinolone Diacetate *(BANM, rINNM)* ⊗

Diacetato de triamcinolona; Triamcinolona, diacetato de; Triamcinolone, Diacetate de; Triamcinoloni Diacetas; Триамцинолона Диацетат.
Triamcinolone 16α,21-diacetate.
$C_{25}H_{31}FO_8$=478.5
CAS — 67-78-7.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — A73MM2Q32P.

Pharmacopoeias. In *US*.

USP 36: (Triamcinolone Diacetate). A fine, white to off-white, crystalline powder, having not more than a slight odour. Practically insoluble in water; soluble 1 in 13 of alcohol, 1 in 80 of chloroform, and 1 in 40 of methyl alcohol; slightly soluble in ether.

Triamcinolone Hexacetonide

(BAN, USAN, rINN) ⊗

CL-34433; Hexacetónido de triamcinolona; TATBA; Triamcinolona, hexacetónido de; Triamcinolone Acetonide 21-(3,3-Dimethylbutyrate); Triamcinolone, Hexacétonide de; Triamcinolon-hexacetonid; Triamcinolonhexacetonid; Triamcinoloni Hexacetonidum; Triamcinolono heksacetonidas; Triamsinoloniheksasetonidi; Триамцинолона Гексацетонид.
9α-Fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxypregna-1,4-diene-3,20-dione 21-(3,3-dimethylbutyrate).
$C_{30}H_{41}FO_7$=532.6
CAS — 5611-51-8.
ATC — A01AC01; C05AA12; D07AB09; H02AB08; R01AD11; R03BA06; S01BA05.
ATC Vet — QA01AC01; QC05AA12; QD07AB09; QH02AB08; QR01AD11; QR03BA06; QS01BA05.
UNII — I7GT1U99Y9.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Triamcinolone Hexacetonide). A white or almost white, crystalline powder. Practically insoluble in water; sparingly soluble in dehydrated alcohol and in methyl alcohol. Protect from light.

USP 36: (Triamcinolone Hexacetonide). A white to cream-coloured powder. Practically insoluble in water; soluble in chloroform; slightly soluble in methyl alcohol.

Uses and Administration

Triamcinolone is a corticosteroid with mainly glucocorticoid activity (p. 1597.1); 4 mg of triamcinolone is equivalent in anti-inflammatory activity to about 5 mg of prednisolone. It is used, either in the form of the free alcohol or in one of the esterified forms, in the treatment of conditions for which corticosteroid therapy is indicated (see p. 1597.3), except adrenocortical insufficiency for which hydrocortisone with supplementary fludrocortisone is preferred.

The dose may be expressed in terms of the base, and the following are each equivalent to about 10 mg of triamcinolone:

- triamcinolone acetonide 11 mg
- triamcinolone acetonide sodium phosphate 14 mg
- triamcinolone diacetate 12 mg
- triamcinolone hexacetonide 14 mg

However, esterification generally alters potency and compounds with equivalent triamcinolone content may not have equivalent clinical effect.

For **oral dosage** triamcinolone is used in doses ranging from 4 to 48 mg daily.

For parenteral use the acetonide ester is given in doses of about 40 to 80 mg by **intramuscular injection**. It is usually given as a suspension to provide a prolonged systemic effect. A single dose of 40 to 100 mg of the acetonide may provide symptomatic control throughout the pollen season for hay fever sufferers (but see Rhinitis, p. 1650.1). The diacetate ester has also been given intramuscularly.

For **intra-articular injection** triamcinolone acetonide, diacetate, and hexacetonide have all been used. Doses for these esters have typically been in the range of 2.5 to 40 mg, depending upon the size of the joint injected.

For **topical application** in the treatment of various skin disorders triamcinolone acetonide is used, usually in creams, lotions, or ointments containing 0.1% although concentrations ranging from 0.025 to 0.5% have been employed. Several topical preparations also contain an antimicrobial drug. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Triamcinolone esters are also commonly used by **intralesional** or **intradermal injection** in the treatment of some inflammatory skin disorders such as keloids. Suggested doses for the various esters have been:

- acetonide: 1 to 3 mg per site with no more than 5 mg injected into any one site or not more than 30 mg in total if several sites of injection are used
- diacetate: a total of 5 to 25 mg, injected as no more than 100 micrograms/cm² of skin surface area
- hexacetonide: up to 500 micrograms per square inch (about 80 micrograms/cm²) of affected skin

In the treatment of allergic rhinitis (p. 1650.1) triamcinolone acetonide may be given by a **nasal spray** in a usual initial dose of 2 sprays (110 micrograms) into each nostril once daily, reduced to 1 spray (55 micrograms) into each nostril once daily when control is achieved.

Preservative-free suspensions of triamcinolone acetonide are available for **intravitreal injection** (see Eye Disorders, below). A dose of 4 mg is used for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions that are unresponsive to topical corticosteroids. Further doses may be given as needed during the course of treatment. A dose of 1 to 4 mg may be used for visualisation during vitrectomy.

For doses used in children, see below.

Other esters of triamcinolone that have occasionally been used include the acetonide dipotassium phosphate, acetonide hemisuccinate, aminobenzal benzamidoisobutyrate, and benetonide. Flupamesone (triamcinolone acetonide metembonate) has also been used.

Administration in children. Triamcinolone acetonide and hexacetonide have been used for **intra-articular injection** in children. Although unlicensed in the UK for use in children under 6 years of age, the *BNFC* includes doses for injection into larger joints in those aged from 1 to 18 years. A dose of triamcinolone acetonide 2 mg/kg may be used, to a usual maximum of 40 mg, or triamcinolone hexacetonide 1 mg/kg to a usual maximum of 20 mg. However, higher doses have been used. Treatment may be repeated for relapse if necessary, although each joint should usually be treated no more than 3 or 4 times in a year.

In the treatment of allergic rhinitis triamcinolone acetonide may be given by a **nasal spray**. Children aged 6 to 12 years may be given 1 spray (55 micrograms) into each nostril once daily. This dose may be increased to 2 sprays (110 micrograms) into each nostril once daily for control of severe symptoms. The lowest effective dose should be used once symptoms have been controlled. In children aged from 2 to 5 years, the recommended and maximum dose is 55 micrograms into each nostril once daily.

Asthma. Corticosteroids and beta$_2$-adrenoceptor agonists form the cornerstone of the management of asthma (see p. 1600.3).

Intramuscular triamcinolone acetonide has been reported to be more effective than oral low-dose prednisone in controlling exacerbations in patients with severe, chronic, life-threatening asthma,[1] although this conclusion is controversial.[2-7]

1. Ogirala RG, *et al.* High-dose intramuscular triamcinolone in severe, chronic, life-threatening asthma. *N Engl J Med* 1991; **324**: 589–9. Correction. *ibid.*; 1380.
2. Salmeron S, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325**: 429–30.
3. Nicholas SS. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325**: 430.
4. Kidney JC, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325**: 430.
5. Capewell S, McLeod DT. Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325**: 430.
6. Ogirala RG, *et al.* Intramuscular triamcinolone in severe asthma. *N Engl J Med* 1991; **325**: 431.
7. Capewell S, McLeod D. Injected corticosteroids in refractory asthma. *Lancet* 1991; **338**: 1075–6.

Chronic obstructive pulmonary disease. Inhaled corticosteroids may be used in chronic obstructive pulmonary disease (see p. 1603.1).

Eye disorders. Intravitreal injection of triamcinolone acetonide has been tried in the management of eye disorders characterised by oedema and the abnormal proliferation of intra-ocular cells. Promising results have been reported in diabetic macular oedema,[1,2] cystoid macular oedema, and oedema associated with retinal vein occlusion.[2-5] It has also been used in age-related macular degeneration (p. 880.2; better results being seen when it is combined with photodynamic therapy), in proliferative diabetic retinopathy, and in the management of some forms of cataract and non-infectious uveitis.[2,3] Complications of treatment may include raised intra-ocular pressure (IOP)[6] and both infectious and non-infectious endophthalmitis.[2] Patients with a baseline IOP greater than 16 mmHg or receiving a second injection should be carefully monitored, as they may be at greater risk of an increase; monitoring should continue beyond 6 months.[6]

Dissolved drugs are not retained in the eye for prolonged periods, and early studies and off-label treatment have used injectable suspensions to achieve long-lasting concentrations of triamcinolone in the vitreous body.[7] However, these commercial products were intended for intramuscular and intra-articular use and not licensed for intravitreal injection, and there has been concern about the potential ocular toxicity of their preservative, benzyl alcohol.[2,7] Various techniques, such as sedimentation, centrifugation, and filtration, have been used extemporaneously to reduce the benzyl alcohol content of such products, but the quantity of triamcinolone in the final preparation may be altered depending on the technique used.[8] More recently, preservative-free products have been licensed in the USA for intravitreal use (*Triesence; Alcon, USA* and *Trivaris; Allergan, USA*—see Uses and Administration, above).

1. Ip MS. Intravitreal injection of triamcinolone: an emerging treatment for diabetic macular edema. *Diabetes Care* 2004; **27**: 1794–7.
2. Jonas JB. Intravitreal triamcinolone acetonide for treatment of intraocular oedematous and neovascular diseases. *Acta Ophthalmol Scand* 2005; **83**: 645–63.

3. van Kooij B, *et al.* The pros and cons of intravitreal triamcinolone injections for uveitis and inflammatory cystoid macular edema. *Ocul Immunol Inflamm* 2006; 14: 73–85.
4. Jonas JB. Intravitreal triamcinolone acetonide: a change in a paradigm. *Ophthalmic Res* 2006; 38: 218–45.
5. Sivaprasad S, *et al.* Intravitreal steroids in the management of macular oedema. *Acta Ophthalmol Scand* 2006; 84: 722–33.
6. Rhee DJ, *et al.* Intraocular pressure alterations following intravitreal triamcinolone acetonide. *Br J Ophthalmol* 2006; 90: 999–1003.
7. Jonas JB. Effects of triamcinolone acetonide injections with and without preservative. *Br J Ophthalmol* 2007; 91: 1099–1101.
8. García-Arumí J, *et al.* Comparison of different techniques for purification of triamcinolone acetonide suspension for intravitreal use. *Br J Ophthalmol* 2005; 89: 1112–14.

Haemangioma. For reference to the use of a mixture of triamcinolone and betamethasone for intralesional injection of haemangioma, see p. 1605.3.

Rhinitis. Triamcinolone is used[1,2] in the management of allergic rhinitis (p. 612.1). However, the use of depot injections of triamcinolone to manage seasonal allergic rhinitis has been deemed unacceptable by some.[3]

1. Jeal W, Faulds D. Triamcinolone acetonide: a review of its pharmacological properties and therapeutic efficacy in the management of allergic rhinitis. *Drugs* 1997; 53: 257–80.
2. Gawchik SM, Saccar CL. A risk-benefit assessment of intranasal triamcinolone acetonide in allergic rhinitis. *Drug Safety* 2000; 23: 309–22.
3. Anonymous. Any place for depot triamcinolone in hay fever? *Drug Ther Bull* 1999; 37: 17–18.

Adverse Effects, Treatment, Withdrawal, and Precautions

As for corticosteroids in general (see p. 1615.3, p. 1618.1, and p. 1618.3, respectively). High doses of triamcinolone may have a greater tendency to produce proximal myopathy. Its effects on sodium and water retention are less than those of prednisolone.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects.

Effects on the eye. For complications and precautions associated with intravitreal use of triamcinolone see under Eye Disorders, p. 1649.3.

Hypersensitivity. Local reactions to topical triamcinolone preparations have been attributed to the content of ethylenediamine.[1,2] However, there have also been reports of anaphylactic shock after intra-articular[3] or intramuscular[4] injection of triamcinolone acetonide.

1. Wright S, Harman RRM. Ethylenediamine and piperazine sensitivity. *BMJ* 1983; 287: 463–4.
2. Freeman S. Allergy to Kenacomb cream. *Med J Aust* 1986; 145: 361.
3. Larsson L. Anaphylactic shock after in administration of triamcinolone acetonide in a 35-year-old female. *Scand J Rheumatol* 1989; 18: 441–2.
4. Gonzalo FE, *et al.* Anaphylactic shock caused by triamcinolone acetonide. *Ann Pharmacother* 1994; 28: 1310.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies triamcinolone as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 17/10/11)

Interactions

The interactions of corticosteroids in general are described on p. 1619.3.

Pharmacokinetics

For a brief outline of the pharmacokinetics of corticosteroids, see p. 1620.3.

Triamcinolone is reported to have a half-life in plasma of about 2 to over 5 hours. It is bound to plasma albumin to a much smaller extent than hydrocortisone.

The acetonide, diacetate, and hexacetonide esters of triamcinolone are only very slowly absorbed from injection sites.

Triamcinolone crosses the placenta.

References to the pharmacokinetics of triamcinolone and its esters.

1. Möllmann H, *et al.* Pharmacokinetics of triamcinolone acetonide and its phosphate ester. *Eur J Clin Pharmacol* 1985; 29: 85–9.
2. Derendorf H, *et al.* Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. *Clin Pharmacol Ther* 1986; 39: 313–17.
3. Derendorf H, *et al.* Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. *J Clin Pharmacol* 1995; 35: 302–5.
4. Argenti D, *et al.* A mass balance study to evaluate the biotransformation and excretion of [^{14}C]-triamcinolone acetonide following oral administration. *J Clin Pharmacol* 2000; 40: 770–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fortcinolona; Glyrop; Kenacort-A; Kenacort; Ledercort; Nasacort; Triamciterap; Triampoen; ***Austral.***: Aristocort; Kenacort-A; Kenalog in Orabase; Telnase; Tricortone; ***Austria***: Nasacort; Solu-Volon A; Volon A; Volon; ***Belg.***: Albicort; Delphi; Kenacort-A; ***Braz.***: Airclin; Azmacort†; Nasacort; Omcilon-A Orabase; Oncicrem-A; Oncileg A; Theracort; Triancil; ***Canad.***: Aristocort; Aristospan; Kenalog; Nasacort; Oracort; Triaderm; ***Chile***: Kenacort-A†; Nasacort; ***China***: A Sai Song (阿赛松); Kenacort-A (康宁克通-A); Kenalog (康宁乐); Nincort (宁康); Xing Rui Ke (星瑞克); Zhen De (珍德); ***Cz.***: Nasacort†; Triamcinolon; ***Denm.***: Kenalog; Lederspan; Nasacort; ***Fin.***: Aftab; Kenacort-T†; Lederspan; Nasacort; ***Fr.***: Hexatrione; Kenacort; Nasacort; ***Ger.***: Aftab; Delphicort; Kortikoid-ratiopharm; Lederlon; Linolacort Triam; Nasacort†; Polcortolon N; Rhinisan; Triam; TriamCreme; Triamgalen; Triamhexal†; TriamSalbe†; Volon A; Volon; Volonimat N; Volonimat; ***Gr.***: Forlion; Kenacort-A; Kenacort; Nasacort; Nasatrim; Senciderm; Triamcinal; ***Hong Kong***: Aftach; Aristo; Dermacort; Kenacort-A†; Kenalog in Orabase†; Nasacort; Oramedy; Shincort; Syncort†; Triam†; ***Hung.***: Ftorocort; Kenalog; Polcortolone; ***India***: Av Cort; Avcort; Comcort; Corurima; D-Cort; Hicort; Hylone; Hynot; Kenacort; Ledercort; Nixcort; Tess; Tricort; ***Indon.***: Amtocort; Flamicort; Kenacort-A; Kenacort; Kenalog in Orabase; Ketricin; Nasacort; Sinocort; Triamcort; Tridez†; Trilac Trinolon; ***Irl.***: Adcortyl in Orabase†; Adcortyl; Kenalog†; Nasacort; ***Israel***: Oracort; Sterocort; Steronase Aq; ***Ital.***: Aftab; Kenacort; Nasacort; Triamvirgi; ***Jpn***: Aftach; MaQaid; ***Malaysia***: Dermacort; Kanolone; Kenalog in Orabase; Metoral; Nasacort AQ; Orrepaste; Shincort; Sivkort; Tramsone; ***Mex.***: ATLC; Azucort†; Intralon; Kenacort; Kenalog Dental; Nasacort; Softram; Triamsicort; Zamacort†; ***Neth.***: Kenacort-A; Nasacort; Zure oordruppels met triamcinolonacetonide; ***Norw.***: Kenacort-T; Lederspan; Nasacort; Triesence; ***NZ***: Aristocort; Kenacort-A; Kenalog in Orabase; Oracort; Telnase; ***Philipp.***: Actonaze; Kanosole; Kenacort-A†; Kenacort†; Shincort; Tricin; Tricort; ***Pol.***: Polcortolon; ***Port.***: Aftach; Nasacort; ***Rus.***: Berlicort (Берликорт)†; Ftorocort (Фторокорт); Kenalog (Кеналог); Polcortolon (Полькортолон); Polcortolon (Полькортолон); Polcortolon TC (Полькортолон TC); Triacort (Триакорт); ***S.Afr.***: Kenalog in Orabase; Nasacor; ***Singapore***: Dermacort†; Kenalog in Orabase; Keno; Nasacort; Oral-T; Oramedy; Orrepaste; Shincort; Tramsone; Triamnone; Trinolone; ***Spain***: Flutenal†; Nasacort; Proctosteroid; Trigon Depot; ***Swed.***: Kenacort-T; Lederspan; Nasacort; ***Switz.***: Kenacort-A Solubile; Kenacort-A; Kenacort; Nasacort; Triamcort; ***Thai.***: Actyl; Aristocort; Betji-Cort; Centocort; Curran; Dynacort; Facort; Ftorocort†; Generlog; Kanolone; Kela; Kelamild; Kemzid; Kena-Lite; Kenacort-A†; Kenalog in Orabase†; Keno; Lala; Laver; Lenicort; Lonna; M-Divate; Manolone; Metoral; Milanolone†; Musaral; Nasacort; Oracortia; Oral-T; Oralog†; Oralpac Orapaste; Orcilone; Paloc; Risto; Shincort; Simacort; T-1†; T-Ora; TA Osoth; Tacinol; Thainocort; Topilone; Tram; Tramsilone; Triama; Trilosil; Trim; Trinoman; TV Lone; Unif†; V Nolone; V-Nolone; Vacinolone; Zyno; ***Turk.***: Artropan; Kenacort-A; Nasacort; Sinakort-A; Triaver; ***UK***: Adcortyl in Orabase†; Adcortyl; Kenalog; Nasacort; ***Ukr.***: Focort (Фокорт); Ftorocort (Фторокорт); Kenalog (Кеналог); Polcortolon (Полькортолон); ***USA***: AllerNaze; Aristospan; Atolone; Azmacort†; Flutex†; Kenalog in Orabase; Kenalog; Kenonel; Nasacort; Oralone Dental†; pediaderm TA; Tac; Tri-Kort; Triacet; Triam-A; Triamonide; Trianex; Triderm; Triesence; Trilog; Trivaris; ***Venez.***: Kenacort; Nasacort.

Multi-ingredient Preparations. *Arg.*: Bagovit A Plus; Biotaer Nasal†; Kenacomb; Mantus; Sorsis; ***Austral.***: Kenacomb; Otocomb Otic; ***Austria***: Aureocort; Pevisone; Volon A antibiotikahaltig†; Volon A Tinktur; ***Belg.***: Mycolog; Pevisone†; Trianal; ***Braz.***: Londerm-N†; Mud; Neolon D; Omcilon-A M; Oncibel; Oncileg; Onciplus†; ***Canad.***: ratio-Triacomb; Viaderm-KC; ***China***: An Long (安隆); Fu Yan Ning (扶严宁); Ji Bai Fu (吉佰芙); Kenacomb (复方康纳乐霜); Pevisone (派瑞松); YiFuQing (益富清); Zhaohuile (朝晖乐); ***Cz.***: Triaderm†; Triamcinolon E; Triamcinolon S; Triamcinolon; ***Denm.***: Kenalog Comp med Mycostatin†; Pevison; Pevisone†; ***Fin.***: Pevisone; ***Fr.***: Cidermex†; Kenalcol†; Localone; Pevisone; ***Ger.***: Epipevisone; Ledermix; Moronal V†; Mykoproct sine†; Volon A Tinktur N; Volon A-Schuttelmix; Volonimat Plus N†; ***Gr.***: Bioderm; Biofloderm; Dermochrom; Kenacomb; Olamyc; Pevison; ***Hong Kong***: Anso; Antiderm†; Centacomb; Clotrinolon; Dermawell†; Ecocort; Inquadeicren; Kenacomb†; Ledermix; Orageslc Pevisone; Tri-Gel†; Triacomb†; Triamecon; Triconazole; Triditol-G; ***Hung.***: Alkcema; Polcortolon TC†; ***India***: Daktarin-T; Exsora; Kenacomb; Kenalog-S; Ledercort-N; Micolon; ***Indon.***: Kenantist†; New Kenacomb†; ***Irl.***: Kenacomb†; Ledermix; ***Israel***: Dermacombin; Ledermix; Oracort E; Pevisone†; ***Ital.***: Assocort†; Aureocort; Dermomycin Cort; Dirahist; Kataval; Pevisone; ***Malaysia***: Aecoras; Ecocort; Econazine; Endix; Kenacomb; Kifugan; Oral-Aid; ***Mex.***: Bidrozil†; Biotriamin†; Kenacomb; Softramc; ***Neth.***: Mycolog†; Trianal; Will-Anal; ***Norw.***: Pevisone; ***NZ***: Kenacomb; Viaderm-KC; ***Philipp.***: Kenacomb†; Nizolex; Oticom; Pevisone; ***Pol.***: Pevisone; Polcortolon TC; Triacomb; ***Port.***: Localone; Pevisone; ***S.Afr.***: Kenacomb†; Pevisone; Trialone†; ***Singapore***: Ecocort; Econazine; Epiderm; Oracort 3; Oral Aid; Pevisone; ***Spain***: Aldoderma; Anasilpiel†; Anso; Cemalyt; Cremsol†; Flutenal Gentamicina†; Flutenal Sali†; Interderm; Nesfare; Positon; ***Swed.***: Kenacombin Novum†; Kenacort-T comp†; Pevisone; ***Switz.***: Kenacort-A; Ledermix; Pevisone; ***Thai.***: Dermacombin; Ecocort; Ecoderm; Econazine; Pungisil-T; KA-Cilone†; Kelaplus; Kenacomb†; Lymarin; Tara-Plus; Timi; Tricozole; Trimicon; ***Turk.***: Aftogel; Ekze-Mant; ***UAE***: Panderm; ***UK***: Aureocort; Ledermix; ***Ukr.***: Trimistin (Тримистин); ***USA***: Myco-Biotic II; Myco-Triacet II; Mycogen II; Mycolog-II; Myconel; NGT; Tri-Statin II; ***Venez.***: Kenacomb; Kenalog.

Used as an adjunct in:. *Rus.*: Prodetoxon (Продетоксон).

Pharmacopoeial Preparations

BP 2014: Triamcinolone Acetonide Injection; Triamcinolone Acetonide Nasal Spray; Triamcinolone Cream; Triamcinolone Hexacetonide Injection; Triamcinolone Ointment; Triamcinolone Oromucosal Paste; Triamcinolone Tablets;

USP 36: Neomycin Sulfate and Triamcinolone Acetonide Cream; Neomycin Sulfate and Triamcinolone Acetonide Ophthalmic Ointment; Nystatin and Triamcinolone Acetonide Cream; Nystatin and Triamcinolone Acetonide Ointment; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream; Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Cream; Triamcinolone Acetonide Dental Paste; Triamcinolone Acetonide Injectable Suspension; Triamcinolone Acetonide Lotion; Triamcinolone Acetonide Ointment; Triamcinolone Acetonide Topical Aerosol; Triamcinolone Diacetate Injectable Suspension Triamcinolone Diacetate Syrup; Triamcinolone Hexacetonide Injectable Suspension; Triamcinolone Tablets.

Ulobetasol Propionate *(rINNM)* ⊗

BMY-30056; CGP-14458; 6-α-Fluoroclobetasol Propionate; Halobetasol Propionate (USAN); Propionato de ulobetasol; Ulobétasol, propionate d'; Ulobetasol, propionato de; Ulobetasoli Propionas; Улобетазола Пропионат.

21-Chloro-6α,9-difluoro-11β,17-dihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17-propionate.

$C_{25}H_{31}ClF_2O_5$=485.0

CAS — 98651-66-2 (ulobetasol); 66852-54-8 (ulobetasol propionate).

ATC — D07AC21.

ATC Vet — QD07AC21.

UNII — 91A0K1TY3Z.

Pharmacopoeias. In *US.*

USP 36: (Halobetasol Propionate). A white to off-white powder. Practically insoluble in water; freely soluble in acetone and in dichloromethane. Store at a temperature of 2 degrees to 8 degrees. Protect from light.

Profile

Ulobetasol propionate is a corticosteroid that is used topically for its glucocorticoid activity (p. 1597.1) in the treatment of various skin disorders. It is usually used as a cream or ointment containing 0.05%.

When applied topically, particularly to large areas, when the skin is broken, or under occlusive dressings, corticosteroids may be absorbed in sufficient amounts to cause systemic effects (p. 1615.3). The effects of topical corticosteroids on the skin are described on p. 1617.3. For recommendations concerning the correct use of corticosteroids on the skin, and a rough guide to the clinical potencies of topical corticosteroids, see p. 1599.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Ultravate; ***India***: Halobeta; Halostrol; Halovate; Hobs; ***USA***: Halonate; Ultravate.

Multi-ingredient Preparations. ***India***: Halostrol-F; Halostrol-M; Halovate-F; Halovate-S; Hobs-S; ***USA***: Halac Kit.

Cough Suppressants Expectorants Mucolytics and Nasal Decongestants

This chapter describes drugs that are used mainly as cough suppressants, expectorants, or mucolytics, and also those sympathomimetics primarily used for the relief of nasal congestion. Other drugs used in cough include antihistamines (p. 610.1), bronchodilators (p. 1195.1), and local anaesthetics (p. 1976.1). Compounds with a demulcent action such as glycerol (p. 2517.2) and sucrose (p. 2096.3) are also used, as are various hydrating inhalations.

Cough suppressants

Cough suppressants have either a central or a peripheral action on the cough reflex or a combination of both. Centrally acting cough suppressants increase the threshold of the cough centre in the brain to incoming stimuli whereas those acting peripherally decrease the sensitivity of the receptors in the respiratory tract. Some drugs have an indirect peripheral mechanism of action and may alter mucociliary factors, exert a local analgesic or anaesthetic action on the receptors, protect the receptors from irritant stimuli, or act as bronchodilators.

Those centrally acting cough suppressants structurally related to morphine that are included in this chapter, such as dextromethorphan, have little or no analgesic action. Those that also have an important analgesic action, such as codeine or diamorphine, are described in the chapter on Analgesics, p. 3.1.

Described in this chapter are

- Acetyldihydrocodeine, p. 1654.3
- Benproperine, p. 1656.2
- Benzonatate, p. 1656.2
- Bibenzonium, p. 1656.3
- Butamirate, p. 1657.3
- Butetamate, p. 1658.1
- Clobutinol, p. 1658.3
- Clofedanol, p. 1659.1
- Cloperastine, p. 1659.2
- Dextromethorphan, p. 1660.1
- Dimemorfan, p. 1661.3
- Dimethoxanate, p. 1661.3
- Dropropizine, p. 1662.2
- Elecampane, p. 1662.3
- Ethyl Orthoformate, p. 1665.3
- Fedrilate, p. 1665.3
- Fominoben, p. 1665.3
- Glaucine, p. 1666.1
- Helicidine, p. 1667.1
- Isoaminile, p. 1668.2
- Morclofone, p. 1669.2
- Nepinalone, p. 1670.2
- Nicocodine, p. 1670.3
- Normethadone, p. 1670.3
- Noscapine, p. 1670.3
- Oxeladin, p. 1671.2
- Oxolamine, p. 1671.2
- Pentoxyverine, p. 1672.1
- Pholcodine, p. 1675.1
- Pipazetate, p. 1675.2
- Poppy Capsule, p. 1675.3
- Prenoxdiazine, p. 1675.3
- Promolate, p. 1676.1
- Sodium Dibunate, p. 1677.3
- Thebacon, p. 1679.1
- Tipepidine, p. 1679.1
- Zipeprol, p. 1680.3

Expectorants

Expectorants are considered to increase the volume of secretions in the respiratory tract thereby facilitating their removal by ciliary action and coughing. Many traditional expectorants, including ipecacuanha, squill, ammonium salts, some volatile oils, and various iodide compounds, have been considered to achieve this by a reflex irritant effect on the gastric mucosa.

Described in this chapter are

- Ammonium Salts, p. 1655.3
- Calcium Iodide, p. 1658.1
- Cocillana, p. 1659.2
- Coltsfoot, p. 1659.2
- Creosote, p. 1659.3
- Elecampane, p. 1662.3
- Eprazinone, p. 1664.3
- Eprozinol, p. 1665.1
- Eriodictyon, p. 1665.2
- Fudosteine, p. 1666.1
- Guacetisal, p. 1666.1
- Guaiacol, p. 1666.1
- Guaietolin, p. 1666.2
- Guaifenesin, p. 1666.2
- Guaimesal, p. 1667.1
- Iodinated Glycerol, p. 1667.2
- Ipecacuanha, p. 1667.2
- Marrubium, p. 1668.3
- Senega Root, p. 1677.2
- Squill, p. 1677.3
- Sulfoguaiacol, p. 1678.1
- Terpin Hydrate, p. 1678.2
- Tolu Balsam, p. 1679.2

Mucolytics

Mucolytics alter the structure of mucus to decrease its viscosity thereby facilitating its removal by ciliary action or expectoration.

Acetylcysteine, carbocisteine, and mecysteine all have thiol groups; if this group is free, as in acetylcysteine, it may be substituted for disulfide bonds in mucus and therefore break the mucus chains. However, drugs such as carbocisteine with 'protected' thiol groups cannot act by this mechanism and their exact mode of action is unclear. Thiol groups are also involved in the mechanism of action of some of these drugs when they are used in the treatment of poisoning.

Deoxyribonucleases such as dornase alfa act as mucolytics by hydrolysing the accumulated extracellular DNA from decaying neutrophils that contributes to the viscous respiratory secretions of cystic fibrosis.

Drugs with **mucoregulatory** actions, typically affecting mucin and chloride secretion by acting on ion channels in the respiratory tract, are also being developed; examples under investigation include denufosol and talniflumate.

Described in this chapter are

- Acetylcysteine, p. 1652.2
- Ambroxol, p. 1654.3
- Bromhexine, p. 1656.3
- Brovanexine, p. 1657.3
- Carbocisteine, p. 1658.1
- Dembrexine, p. 1659.3
- Denufosol, p. 1660.1
- Dornase Alfa, p. 1662.1
- Eprazinone, p. 1664.3
- Eprozinol, p. 1665.1
- Erdosteine, p. 1665.1
- Ethyl Cysteine Hydrochloride, p. 1665.2
- Mecysteine, p. 1669.1
- Methyl Dacisteine, p. 1669.2
- Neltenexine, p. 1670.2
- Sobrerol, p. 1677.2
- Talniflumate, p. 1678.2
- Telmesteine, p. 1678.2

Sympathomimetics

Sympathomimetics described in this chapter may be used systemically (such as phenylephrine) or locally (such as naphazoline), for their alpha agonist actions to produce vasoconstriction of the nasal mucosa, thus relieving congestion. Others such as ephedrine have both alpha and beta agonist actions. The beta agonist actions confer upon them bronchodilating properties, but they have been superseded as bronchodilators by the more selective $beta_2$ agonists such as salbutamol. The value of bronchodilators in non-asthmatic cough has not been confirmed.

Described in this chapter are

- Amidefrine, p. 1655.3
- Clonazoline, p. 1659.1
- Ephedra, p. 1663.1
- Ephedrine, p. 1663.1
- Etafedrine, p. 1665.2
- Fenoxazoline, p. 1665.3
- Indanazoline, p. 1667.1
- Levmetamfetamine, p. 1668.3
- Methoxyphenamine, p. 1669.1
- Methylephedrine, p. 1669.2
- Naphazoline, p. 1669.3
- Oxymetazoline, p. 1671.3
- Phenylephrine, p. 1672.2
- Phenylpropanolamine, p. 1674.1
- Pseudoephedrine, p. 1676.1
- Tetryzoline, p. 1678.3
- Tramazoline, p. 1679.3
- Tuaminoheptane, p. 1679.3
- Tymazoline, p. 1679.3
- Xylometazoline, p. 1680.1

Cough

Cough is an important physiological protective mechanism, but may also occur as a symptom of an underlying disorder such as asthma, gastro-oesophageal reflux disease, and postnasal drip. Treatment of the disorder often alleviates the cough, but there are times when symptomatic treatment is appropriate. The treatment chosen depends on whether the cough is productive or non-productive.[1-11]

A **non-productive cough** such as that often seen with the common cold serves no useful purpose for the patient, and cough suppressants may provide some relief, particularly if given at night.

- Of the commonly used *cough suppressants*, pholcodine and dextromethorphan are considered to have fewer adverse effects than codeine. However, there is little evidence that these drugs are effective in severe cough.
- Sedating *antihistamines* such as diphenhydramine are frequently used as cough suppressants in compound preparations. Suggested mechanisms of action have included reduction in cholinergic nerve transmission, or cough suppression as a result of their sedative effects. Antihistamines reduce nasal secretions and may be of value in treating cough caused by postnasal drip, particularly if associated with allergic rhinitis (see p. 612.1). However, they should not be used to treat a productive cough because they may cause formation of viscid mucus plugs. Their sedative effects are a disadvantage for daytime use but may be a short-term advantage for night coughs.
- *Demulcents* probably act as indirect peripherally acting cough suppressants by providing a protective coating over sensory receptors in the pharynx. Demulcents include glycerol, honey, liquorice, and sucrose syrups.

A potent cough suppressant such as morphine is needed for the relief of **intractable cough** in terminal illness. The use of such a potent opioid is not otherwise considered appropriate for cough.

- *Local anaesthetics* such as lidocaine or bupivacaine have been inhaled in severe intractable cough, including cough caused by malignant neoplasms. Cough suppression is produced by an indirect peripheral action on sensory receptors, but as all protective pulmonary reflexes may be lost and bronchospasm may be induced, such treatment should be used with care. There may also be temporary loss of the swallowing reflex.

A **productive cough** is characterised by the presence of sputum and may be associated with conditions such as chronic bronchitis, bronchiectasis, or cystic fibrosis. Cough suppressants are inappropriate, since the cough serves the purpose of clearing the airways, but expectorants have been used on the grounds that increasing the volume of secretions in the respiratory tract facilitates removal by ciliary action and coughing. However, clinical evidence of efficacy is lacking, and many authorities consider expectorants to be of no value other than as a placebo.

- Commonly used *expectorants* include ammonium salts, guaifenesin, ipecacuanha, and sodium citrate. Iodides have also been used but there has been concern over their safety for prolonged use in respiratory disorders and because of their potential for thyroid suppression; in particular, it has been recommended that they should not be given to children, adolescents, pregnant women, or patients with goitre.
- *Mucolytics* have been shown to affect sputum viscosity and structure and patients have reported alleviation of their symptoms, but no consistent improvement in lung function has been found. Commonly used mucolytics include acetylcysteine, bromhexine, carbocisteine, and mecysteine. Dornase alfa is also available, in particular for patients with cystic fibrosis. In theory mucolytics may disrupt the gastric mucosal barrier and caution has been recommended in patients with a history of peptic ulcer disease.
- *Hydrating agents* liquefy mucus and also have a demulcent effect. Hydration may be achieved simply by inhaled warm moist air. The addition of substances such as menthol, benzoin, or volatile oils is unlikely to provide any additional benefit but may encourage the use of such inhalations. Inhaled aerosols of water, sodium bicarbonate, sodium chloride, surfactants such as tyloxapol, osmotic agents such as mannitol, and proteolytic enzymes such as chymotrypsin and trypsin, have also been used for their reported hydrating or mucolytic effects on respiratory secretions.

Cough may sometimes be associated with **bronchospasm** in patients with asthma.

- *Bronchodilators* such as salbutamol (a $beta_2$ agonist) or ipratropium (an antimuscarinic) alleviate cough associated with bronchospasm. However, they are not generally considered of benefit in other forms of cough, and hence are not recommended other than in asthma or selected patients with chronic obstructive pulmonary disease.

Cough and cold preparations containing various combinations of cough suppressants and/or expectorants, with sympathomimetics, antihistamines, or analgesics are available. Some combinations, such as a cough suppressant and an expectorant, seem illogical and have little evidence to support their efficacy. As with many combinations, doses of individual drugs may be inadequate or inappropriate, and the large number of ingredients may expose the patient to unnecessary adverse effects. In particular, concern has been expressed about the safety in *children* of cough and cold preparations that contain antihistamines, cough suppressants, expectorants, and sympathomimetic decongestants, either alone or in combination. A systematic review[12] has found no good evidence for or against the efficacy of over-the-counter (OTC) preparations in acute cough. The British Thoracic Society considers that OTC medications are as effective as placebo for acute cough with head colds in children.[13] In early 2008, the FDA[14] and MHRA[15] both advised that OTC cough and cold preparations should not be given to children under 2 years of age. They warned of the potential for serious and potentially life-threatening adverse effects and that such preparations provided only symptomatic relief, at best. They also advised that if these products were to be used in children older than 2 years of age, the recommended dose should be followed carefully and measured accurately, and that only one preparation should be used to avoid overdosage of the same drug or similar drugs. A review by the FDA of the use of such preparations in older children (2 to 11 years of age) is ongoing. However, in October 2008, most US manufacturers voluntarily revised the labelling of OTC cough and cold preparations to state not for use in children aged under 4 years.[16] In early 2009, after further review, the MHRA[17] advised that OTC cough and

cold preparations should not be given to children under 6 years of age as there was no robust evidence of their efficacy and because they can cause adverse effects such as allergic reactions, sleep disturbances, and hallucinations. In those aged from 6 to 12 years, such preparations should only be used as second-line therapy and for no more than 5 days; the MHRA also considered that further research is warranted in this age group. Subsequently, additional restrictions have been imposed on the use of OTC cough and cold preparations containing codeine in those aged 18 years and under (see Cough under Codeine, p. 41.1).

To alleviate symptoms of coughs and colds in children aged under 6 years, the MHRA[17] recommends using single-constituent paracetamol or ibuprofen, simple cough preparations (such as those containing glycerol or honey and lemon), vapour rubs and inhalant decongestants (that can be applied to clothing), and, particularly in infants, sodium chloride nasal drops.

1. Irwin RS, Madison JM. The diagnosis and treatment of cough. *N Engl J Med* 2000; 343: 1715–21.
2. Morice AH, Kastelik JA. Chronic cough in adults. *Thorax* 2003; 58: 901–7.
3. de Jongste JC, Shields MD. Chronic cough in children. *Thorax* 2003; 58: 998–1003.
4. Fontana GA, Pistolesi M. Chronic cough and gastro-oesophageal reflux. *Thorax* 2003; 58: 1092–5.
5. Dicpinigaitis PV. Cough in asthma and eosinophilic bronchitis. *Thorax* 2004; 59: 71–2.
6. Belvisi MG, Geppetti P. Cough 7: current and future drugs for the treatment of cough. *Thorax* 2004; 59: 438–40.
7. Morice AH, *et al.* The diagnosis and management of chronic cough. *Eur Respir J* 2004; 24: 481–92.
8. Irwin RS, *et al.* American College of Chest Physicians. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129 (suppl): 1S–23S. Also available at: http://www.chestjournal.org/cgi/reprint/129/1_suppl/1S.pdf (accessed 11/05/07)
9. Bolser DC. American College of Chest Physicians. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. *Chest* 2006; 129 (suppl): 238S–249S. Also available at: http://www.chestjournal.org/cgi/reprint/129/1_suppl/238S.pdf (accessed 11/05/07)
10. Morice AH, *et al.* British Thoracic Society Cough Guideline Group. BTS Guidelines: Recommendations for the management of cough in adults. *Thorax* 2006; 61 (suppl): i1–i24. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/coughguidelinesaugust06.pdf (accessed 15/07/08)
11. Pavord ID, Chung KF. Management of chronic cough. *Lancet* 2008; 371: 1375–84.
12. Smith SM, *et al.* Over-the-counter medications for acute cough in children and adults in ambulatory settings. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 16/04/08).
13. Shields MD, *et al.* British Thoracic Society Cough Guideline Group. BTS guidelines: Recommendations for the assessment and management of cough in children. *Thorax* 2008; 63 (suppl III): iii1–iii19. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Cough/Guidelines/cough_in_children.pdf (accessed 15/07/08)
14. FDA. FDA releases recommendations regarding use of over-the-counter cough and cold products (issued 17th January, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116839.htm (accessed 17/08/10)
15. MHRA/CHM. Updated advice—over-the-counter cough and cold medicines for children. *Drug Safety Update* 2008; 1 (9): 9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014506&RevisionSelectionMethod=Latest (accessed 15/04/08)
16. FDA. FDA statement following CHPA's announcement on nonprescription over-the-counter cough and cold medicines in children (issued 8th October, 2008). Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116964.htm (accessed 17/08/10)
17. MHRA. Press release: better medicines for children's coughs and colds (issued 28th February, 2009). Available at: http://www.mhra.gov.uk/NewsCentre/Pressreleases/CON038902 (accessed 06/04/09) See also: MHRA/CHM. Over-the-counter cough and cold medicines for children. *Drug Safety Update* 2009; 2 (9): 8–9. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON043810&RevisionSelectionMethod=LatestReleased (accessed 17/08/10)

Nasal congestion

Nasal congestion is frequently a symptom of conditions such as rhinitis (p. 612.1), treatment of which can include the use of antihistamines, sympathomimetics, corticosteroids, antimuscarinics, and cromoglicate or nedocromil.

Sympathomimetics are also widely used as nasal decongestants to provide symptomatic relief of the common cold (p. 951.1). They are used for the vasoconstriction produced by their alpha-adrenergic effects; redistribution of local blood flow reduces oedema of the nasal mucosa, thus improving ventilation, drainage, and nasal stuffiness. Sympathomimetics such as ephedrine, phenylephrine, naphazoline, oxymetazoline, and xylometazoline can be used topically as nasal drops or sprays. Those such as pseudoephedrine are given orally. Over-the-counter cough and cold preparations containing sympathomimetic decongestants should be used with caution in children and generally avoided in young children, for details see p. 1651.2.

Topical use, particularly if prolonged, may lead to rebound congestion as vasodilatation becomes prominent and the effects of vasoconstriction subside. Use is therefore restricted to periods of not more than 7 consecutive days. Oral use is not associated with such rebound congestion, but is more likely to be associated with systemic adverse effects and a higher risk of drug interactions. A systematic review found no difference in efficacy between oral and topical decongestants from the limited evidence available.[1]

The benefits of *antihistamines* in nasal congestion other than that associated with allergic rhinitis are doubtful, particularly by topical application.

Inhalations of warm moist air are also useful in the treatment of nasal congestion associated with the common cold. As in the case of cough (see p. 1651.2) the addition of substances such as menthol, benzoin, or volatile oils may encourage the use of such inhalations. Sodium chloride nasal drops may also be effective, particularly in infants and young children.

1. Taverner D, Latte GJ. Nasal decongestants for the common cold. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2009 [Withdrawn] (accessed 14/08/10).

Acetylcysteine *(BAN, USAN, rINN)*

S052; Acetilcisteína; Acetilcisteinas; Acetilcisztein; Acetylcysteïn; Acétylcystéine; Acetylcysteinum; Asetilsistein; Asetyylikysteiini; NSC-111180; Ацетилцистеин.

N-Acetyl-L-cysteine.

$C_5H_9NO_3S$=163.2

CAS — 616-91-1.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

UNII — WYQ7N0BPYC.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Acetylcysteine). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; practically insoluble in dichloromethane. A 1% solution in water has a pH of 2.0 to 2.8. Protect from light.

USP 36: (Acetylcysteine). A white crystalline powder having a slight acetic odour. Soluble 1 in 5 of water and 1 in 4 of alcohol; practically insoluble in chloroform and in ether. pH of a 1% solution in water is between 2.0 and 2.8. Store in airtight containers.

Incompatibility. Acetylcysteine is incompatible with some metals, including iron and copper, with rubber, and with oxygen and oxidising substances. Some antimicrobials including amphotericin B, ampicillin sodium, erythromycin lactobionate, and some tetracyclines are either physically incompatible with, or may be inactivated on mixture with, acetylcysteine.

Stability. A change in colour of solutions of acetylcysteine to light purple does not indicate significant impairment of safety or efficacy.

Acetylcysteine Sodium *(BANM, rINNM)*

Acetilcisteína sódica; Acétylcystéine Sodique; Natrii Acetylcysteinum; Натрий Ацетилцистеин.

$C_5H_8NNaO_3S$=185.2

CAS — 19542-74-6.

ATC — R05CB01; S01XA08; V03AB23.

ATC Vet — QR05CB01; QS01XA08; QV03AB23.

UNII — NRD80R06FB.

Uses and Administration

Acetylcysteine is a mucolytic that reduces the viscosity of secretions probably by the splitting of disulfide bonds in mucoproteins. Since this action is greatest at a pH of 7 to 9, commercial preparations may have had their pH adjusted with sodium hydroxide. It is sometimes stated that acetylcysteine sodium is used, although the dose is expressed in terms of acetylcysteine.

Acetylcysteine is also able to promote the detoxification of an intermediate paracetamol metabolite, and has a key role in the management of paracetamol overdosage.

Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough (p. 1653.3). It can be given by nebulisation of 3 to 5 mL of a 20% solution or 6 to 10 mL of a 10% solution through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution or 2 to 20 mL of a 10% solution may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour. Mechanical suction of the liquefied secretions may be necessary, and nebulisers containing iron, copper, or rubber components should not be used.

Acetylcysteine as a mucolytic is also given orally, as lozenges, or as granules or effervescent tablets dissolved in water, in a usual dose of 600 mg daily as a single dose or in 3 divided doses.

In the treatment of **dry eye** (p. 2190.1) associated with abnormal mucus production, acetylcysteine, usually as a 5% solution with hypromellose, is given topically 3 or 4 times daily. Higher concentrations have been used in some centres.

Acetylcysteine is given by intravenous infusion or orally in the treatment of **paracetamol poisoning** (p. 1653.2).

- If given intravenously: 150 mg/kg (maximum of 16.5 g) of acetylcysteine in 200 mL of glucose 5% is given initially over 60 minutes. This is followed by infusion of 50 mg/kg (maximum of 5.5 g) in 500 mL of glucose 5% over the next 4 hours and then 100 mg/kg (maximum of 11 g) in one litre of glucose 5% over the next 16 hours. Sodium chloride 0.9% may be used where glucose 5% is unsuitable.
- If given orally: an initial dose of 140 mg/kg as a 5% solution is followed by 70 mg/kg every 4 hours for an additional 17 doses.

Acetylcysteine is reported to be most effective when given within 8 hours of paracetamol overdosage, with the protective effect diminishing after this time. However, starting treatment with acetylcysteine later (up to and beyond 24 hours) may still be of benefit.

Acetylcysteine may be used for the treatment of idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1653.1).

For doses in children, see below.

Reviews.

1. Atkinson MG. The use of N-acetylcysteine in intensive care. *Crit Care Resusc* 2002; 4: 21–7.
2. Dekhuijzen PNR. Antioxidant properties of *N*-acetylcysteine: their relevance in relation to chronic obstructive pulmonary disease. *Eur Respir J* 2004; 23: 629–36.
3. Guerin J-C, *et al.* Le stress oxydatif en pathologie broncho-pulmonaire: apport de la N-acétyl-cystéine (NAC). *Rev Pneumol Clin* 2005; 61: 16–21.
4. Aitio M-L. N-acetylcysteine—passe-partout or much ado about nothing? *Br J Clin Pharmacol* 2006; 61: 5–15.
5. Dekhuijzen PN. Acetylcysteine in de behandeling van ernstige COPD. *Ned Tijdschr Geneeskd* 2006; 150: 1222–6.

Administration in children. Acetylcysteine is used for its **mucolytic** activity in respiratory disorders associated with productive cough. Doses in children are similar to adults; 3 to 5 mL of a 20% solution, or 6 to 10 mL of a 10% solution, may be nebulised through a face mask or mouthpiece 3 or 4 times daily. If necessary 1 to 10 mL of a 20% solution, or 2 to 20 mL of a 10% solution, may be given by nebulisation every 2 to 6 hours. It can also be given by direct endotracheal instillation of 1 to 2 mL of a 10 to 20% solution as often as every hour.

Acetylcysteine has also been given orally in a variety of dosage forms. Licensed doses and age ranges vary somewhat from country to country and even from preparation to preparation. For example, in France, children may be given the following doses:

- 1 month to 2 years: 100 mg twice daily
- 2 to 7 years: 200 mg twice daily
- 7 years and over: 200 mg 3 times daily (adult dose)

In Germany and Switzerland, however, a more typical dose for children under 2 years of age is 50 mg two or three times daily.

Acetylcysteine has been used to treat meconium ileus in neonates and distal obstruction syndrome in children with **cystic fibrosis**, although the *BNFC* states that evidence of its efficacy is lacking. Such use is not licensed in the UK, but if it is to be used the *BNFC* suggests an oral dose of acetylcysteine 200 to 400 mg up to 3 times daily if necessary for meconium ileus in neonates. For the *treatment* of distal intestinal obstruction syndrome in children with cystic fibrosis, a single oral dose is recommended as follows:

- 1 month to 2 years: 0.4 to 3 g
- 2 to 7 years: 2 to 3 g
- 7 to 18 years: 4 to 6 g

For the *prevention* of distal intestinal obstruction syndrome, it is recommended to be given orally as follows:

- 1 month to 2 years: 100 to 200 mg 3 times daily
- 2 to 12 years: 200 mg 3 times daily
- 12 to 18 years: 200 to 400 mg 3 times daily

The injection may be used orally, diluted to a concentration of 50 mg/mL; orange or black currant juice or cola may be used as diluents to mask the bitter taste.

In the treatment of **dry eye** associated with tear deficiency, or impaired or abnormal mucus production, acetylcysteine 5% eye drops with hypromellose may be applied, as in adults, 3 or 4 times daily.

Acetylcysteine is given by intravenous infusion or orally in the treatment of **paracetamol poisoning.** Doses for children, including neonates, are similar to adults (see also Uses and Administration, above and Overdosage on p. 116.2), although the volume of intravenous fluid is modified. The *BNFC* suggests the following *intravenous* doses, according to body-weight:

- under 20 kg: initially 150 mg/kg in 3 mL/kg glucose 5% given over 60 minutes, followed by 50 mg/kg in 7 mL/kg glucose 5% given over 4 hours, then 100 mg/kg in 14 mL/kg glucose 5% given over 16 hours
- 20 to 40 kg: initially 150 mg/kg in 100 mL glucose 5% given over 60 minutes, followed by 50 mg/kg in 250 mL glucose 5% given over 4 hours, then 100 mg/kg in 500 mL glucose 5% given over 16 hours
- over 40 kg: adult dose

In the USA, the following *oral* dose is licensed for use in children: 140 mg/kg initially, followed by 70 mg/kg every 4 hours for an additional 17 doses.

Anxiety disorders. In a small 12-week double-blind study,[1] oral acetylcysteine (range 1.2 to 2.4 g daily) produced greater improvement in symptoms of hair-pulling than placebo in patients with trichotillomania.

1. Grant JE, *et al.* N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: a double-blind, placebo-controlled study. *Arch Gen Psychiatry* 2009; 66: 756–63.

Aspergillosis. Although it is not one of the standard therapies discussed on p. 563.1, local instillation of acetylcysteine into the cavity containing the fungus ball has been used to treat aspergilloma.[1] There is some evidence *in vitro* that acetylcysteine has inhibitory properties against *Aspergillus* and *Fusarium* spp.[2]

1. Kauffman CA. Quandary about treatment of aspergillomas persists. *Lancet* 1996; 347: 1640.
2. De Lucca AJ, *et al.* N-Acetylcysteine inhibits germination of conidia and growth of Aspergillus spp. and Fusarium spp. *Antimicrob Agents Chemother* 1996; 40: 1274–6.

Burns. Children with smoke inhalation injury (p. 1683.1) who were treated with aerosolised heparin 5000 units alternating with 3 mL of 20% acetylcysteine solution, inhaled every 2 hours for the first 7 days after injury, appeared to have significantly reduced mortality and reintubation rates compared with historical controls.[1]

1. Desai MH, *et al.* Reduction in mortality in pediatric patients with inhalation injury with aerosolized heparin/N-acetylcystine [sic] therapy. *J Burn Care Rehabil* 1998; 19: 210–12. Correction. *ibid.* 1999; 20: 49.

Cystic fibrosis. Mucolytics such as acetylcysteine are generally not considered[1] to be effective in treating the pulmonary manifestations of cystic fibrosis (p. 177.2).

Meconium ileus equivalent (bowel obstruction due to abnormally viscid contents of the terminal ileum and right colon[2]) in patients with cystic fibrosis has largely disappeared with the use of pancreatic enzymes but may occur when insufficient doses are given;[3] mild cases may be treated with acetylcysteine.[3] Doses of 10 mL of a 20% solution of acetylcysteine have been given orally 4 times daily with 100 mL of a 10% solution of acetylcysteine given as an enema up to 4 times daily depending on the degree of the obstruction.[2]

For suggested children's doses in meconium ileus and distal obstruction syndrome, see Administration in Children, p. 1652.3.

1. Duijvestijn YC, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatr* 1999; 88: 38–41.
2. Hanly JG, Fitzgerald MX. Meconium ileus equivalent in older patients with cystic fibrosis. *BMJ* 1983; 286: 1411–13.
3. David TJ. Cystic fibrosis. *Arch Dis Child* 1990; 65: 152–7.

Interstitial lung disease. Acetylcysteine with prednisolone and azathioprine is a recommended option for the treatment of idiopathic pulmonary fibrosis (see Interstitial Lung Disease, p. 1607.1). In a randomised controlled study, adjunctive oral treatment with acetylcysteine 600 mg three times daily slowed the loss of vital lung capacity compared with standard therapy with azathioprine and prednisone.[1]

1. Demedts M, *et al.* High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005; 353: 2229–42.

Kidney disorders. Acetylcysteine has been reported to improve kidney function in patients with the hepatorenal syndrome and may offer a potential bridging therapy in such patients awaiting liver transplantation.[1] It has also been used in the prevention of contrast media-induced nephrotoxicity in patients with chronic renal impairment, but evidence of benefit is conflicting and its role remains to be established; see Effects on the Kidney under Amidotrizoic Acid (p. 1582.2) for further details.

1. Holt S, *et al.* Improvement in renal function in hepatorenal syndrome with N-acetylcysteine. *Lancet* 1999; 353: 294–5.

Liver disorders. Although benefit has been reported from studies of acetylcysteine in acute liver failure,[1] and some have suggested that it may be useful in preventing tissue hypoxia in patients with acute liver failure receiving vasopressors,[2] studies have mainly been small and clinical outcomes are not well studied.[1] It does not appear to be of benefit in patients undergoing orthotopic liver transplantation.[3,4]

For reference to use in the hepatorenal syndrome, see Kidney Disorders, above. For use in paracetamol-induced liver damage, see Overdosage, under Paracetamol, p. 116.2.

1. Sklar GE, Subramaniam M. Acetylcysteine treatment for non-acetaminophen-induced acute liver failure. *Ann Pharmacother* 2004; 38: 498–501.
2. Caracenl P, Van Thiel DH. Acute liver failure. *Lancet* 1995; 345: 163–9.
3. Bromley PN, *et al.* Effects of intraoperative N-acetylcysteine in orthotopic liver transplantation. *Br J Anaesth* 1995; 75: 352–4.
4. Steib A, *et al.* Does N-acetylcysteine improve hemodynamics and graft function in liver transplantation? *Liver Transpl Surg* 1998; 4: 152–7.

Meconium ileus. For the use of acetylcysteine in infants with meconium ileus, see Cystic Fibrosis, above.

Myocardial infarction. Some studies suggest that addition of intravenous acetylcysteine to thrombolytic therapy in patients with acute myocardial infarction (p. 1257.1) may be of benefit.[1,2] The value of acetylcysteine as an adjunct in patients with or at risk of myocardial infarction has been reviewed.[3,4]

1. Arstall MA, *et al.* N-Acetylcysteine in combination with nitroglycerin and streptokinase for the treatment of evolving acute myocardial infarction: safety and biochemical effects. *Circulation* 1995; 92: 2855–62.
2. Sochman J, *et al.* Infarct size limitation: acute N-acetylcysteine defense (ISLAND trial): preliminary analysis and report after the first 30 patients. *Clin Cardiol* 1996; 19: 96–100.
3. Marchetti G, *et al.* Use of N-acetylcysteine in the management of coronary artery diseases. *Cardiologia* 1999; 44: 633–7.
4. Sochman J. N-acetylcysteine in acute cardiology: 10 years later: what do we know and what would we like to know?! *J Am Coll Cardiol* 2002; 39: 1422–8.

Nitrate tolerance. Acetylcysteine appears to be able to potentiate the peripheral and coronary effects of glyceryl trinitrate.[1] While some studies[2-5] have suggested that acetylcysteine can reverse tolerance to nitrates in patients with coronary heart disease or heart failure, others have failed to find any benefit,[6] although there may be a specific subgroup of responders.[5] The various attempts at overcoming nitrate tolerance are discussed on p. 1394.1.

1. Horowitz JD, *et al.* Combined use of nitroglycerin and N-acetylcysteine in the management of unstable angina pectoris. *Circulation* 1988; 77: 787–94.
2. Packer M, *et al.* Prevention and reversal of nitrate tolerance in patients with congestive heart failure. *N Engl J Med* 1987; 317: 799–804.
3. May DC, *et al.* In vivo induction and reversal of nitroglycerin tolerance in human coronary arteries. *N Engl J Med* 1987; 317: 805–9.
4. Boesgaard S, *et al.* Preventive administration of intravenous N-acetylcysteine and development of tolerance to isosorbide dinitrate in patients with angina pectoris. *Circulation* 1992; 85: 143–9.
5. Pizzulli L, *et al.* N-acetylcysteine attenuates nitroglycerin tolerance in patients with angina pectoris and normal left ventricular function. *Am J Cardiol* 1997; 79: 28–33.
6. Hogan JC, *et al.* Chronic administration of N-acetylcysteine fails to prevent nitrate tolerance in patients with stable angina pectoris. *Br J Clin Pharmacol* 1990; 30: 573–7.

Poisoning and toxicity. Acetylcysteine has been studied for the potential treatment of many forms of toxicity,[1] but only treatment of acute paracetamol poisoning is widely accepted.

1. Chyka PA, *et al.* Utility of acetylcysteine in treating poisonings and adverse drug reactions. *Drug Safety* 2000; 22: 123–48.

CARBON TETRACHLORIDE. The treatment of carbon tetrachloride poisoning is discussed on p. 2175.1. Reports suggest that prompt intravenous therapy with acetylcysteine may help to minimise hepatorenal damage in acute poisoning with carbon tetrachloride.[1,2] When added to supportive therapy the initial dosage regimen should be the same as that used for paracetamol poisoning but as carbon tetrachloride has a much longer half-life than paracetamol, the duration of treatment may need to be increased.[3]

1. Ruprah M, *et al.* Acute carbon tetrachloride poisoning in 19 patients: implications for diagnosis and treatment. *Lancet* 1985; i: 1027–9.
2. Mathieson PW, *et al.* Survival after massive ingestion of carbon tetrachloride treated by intravenous infusion of acetylcysteine. *Hum Toxicol* 1985; 4: 627–31.
3. Meredith TJ, *et al.* Diagnosis and treatment of acute poisoning with volatile substances. *Hum Toxicol* 1989; 8: 277–86.

PARACETAMOL. Acetylcysteine is usually the antidote of choice for paracetamol overdosage (p. 116.2). The intravenous route is favoured in the UK, despite possible anaphylactic reaction, mainly because of concerns over the effects of vomiting and activated charcoal on oral absorption.[1] In the USA the oral route has conventionally been used, despite the unpleasant odour and taste of acetylcysteine solutions, with no evident reduction in effect by charcoal.[2,3] The intravenous route is now also licensed in the USA. Oral and intravenous formulations appear to be equally effective.[4] A disadvantage of the oral route is therapeutic failure in those patients who develop nausea and vomiting, which occurs in most patients with severe poisoning; delays in absorption may also be of concern especially when the end of the critical 8-hour interval is approaching. However, with oral doses, the whole absorbed dose passes through the liver, producing high local concentrations at the site of toxicity.[5] Some consider the intravenous route to be more reliable, and to require fewer doses and a shorter duration of treatment.[6] The major disadvantage of intravenous use is possible anaphylactic reaction. Although these reactions are considered uncommon in patients with paracetamol poisoning, rare fatalities have been reported, and patients with asthma appear to be at particular risk (see also under Precautions, p. 1654.1).[5] Some infuse the first dose of acetylcysteine over 60 minutes instead of 15 minutes[6] in order to reduce the incidence and severity of reactions. However, a multicentre, randomised study found no reduction in adverse outcomes with a 60-minute infusion compared with an infusion period of 15 minutes.[7] It has been suggested that intravenous acetylcysteine may be preferred in those patients with severe poisoning, who present late, who have nausea and vomiting, or who have problems with absorption. Oral use might be preferred in those who present early with uncomplicated mild to moderate poisoning, or who have asthma.[5,8] Whichever route is given, the interval is considered the single most important factor for the prevention of severe hepatic damage.[4,5]

1. Vale JA, Proudfoot AT. Paracetamol (acetaminophen) poisoning. *Lancet* 1995; 346: 547–52.
2. Bowden CA, Krenzelok EP. Clinical applications of commonly used contemporary antidotes: a US perspective. *Drug Safety* 1997; 16: 9–47.
3. Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med* 2008; 359: 285–92.
4. Brok J, *et al.* Interventions for paracetamol (acetaminophen) overdose. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 13/10/06).
5. Prescott L. Oral or intravenous *N*-acetylcysteine for acetaminophen poisoning? *Ann Emerg Med* 2005; 45: 409–13.
6. Anonymous. Acetylcysteine (Acetadote) for acetaminophen overdosage. *Med Lett Drugs Ther* 2005; 47: 70–1.
7. Kerr F, *et al.* The Australasian Clinical Toxicology Investigators Collaboration randomized trial of different loading infusion rates of N-acetylcysteine. *Ann Emerg Med* 2005; 45: 402–8.
8. Kanter MZ. Comparison of oral and i.v. acetylcysteine in the treatment of acetaminophen poisoning. *Am J Health-Syst Pharm* 2006; 63: 1821–7.

Respiratory disorders. Acetylcysteine has been used as a mucolytic in a variety of respiratory disorders associated with productive cough (p. 1651.2). Although there is controversy over the benefits of mucolytics in treating chronic bronchitis or chronic obstructive pulmonary disease (COPD), there is some evidence that they may reduce exacerbations (see p. 1199.1). However, a double-blind multicentre study in patients with COPD failed to find evidence that oral acetylcysteine 600 mg daily reduced exacerbations;[1] as with most other interventions in this condition, it could also not be shown to reduce the rate of decline in lung function.

For the use of aerosolised heparin and acetylcysteine to treat smoke inhalation injury, see Burns, above. It has been suggested that intravenous acetylcysteine might also be of use in acute respiratory distress syndrome (ARDS—p. 1599.3),[2] possibly due to its action as a free radical scavenger,[2,3] but controlled studies in established ARDS failed to show benefit.[4,5]

Acetylcysteine may be used in idiopathic pulmonary fibrosis (see Interstitial Lung Disease, above). See also above for the use of acetylcysteine in the management of cystic fibrosis.

1. Decramer M, *et al.* Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005; 365: 1552–60.
2. Bernard GR. Potential of N-acetylcysteine as treatment for the adult respiratory distress syndrome. *Eur Respir J* 1990; 3 (suppl 11): 496S–498S.
3. Skolnick A. Inflammation-mediator blockers may be weapons against sepsis syndrome. *JAMA* 1990; 263: 930–1.
4. Jepsen S, *et al.* Antioxidant treatment with N-acetylcysteine during adult respiratory distress syndrome: a prospective, randomized, placebo-controlled study. *Crit Care Med* 1992; 20: 918–23.
5. Domenighetti G, *et al.* Treatment with N-acetylcysteine during acute respiratory distress syndrome: a randomized, double-blind, placebo-controlled clinical study. *J Crit Care* 1997; 12: 177–82.

Scleroderma. Acetylcysteine has also been reported to be of benefit in Raynaud's syndrome resulting from scleroderma (see p. 1938.3).

Adverse Effects

Hypersensitivity reactions have been reported in patients receiving acetylcysteine, including bronchospasm, angioedema, rashes and pruritus; hypotension, or occasionally hypertension, may occur. Other adverse effects reported with acetylcysteine include flushing, nausea and vomiting, fever, syncope, sweating, arthralgia, blurred vision, disturbances of liver function, acidosis, convulsions, and cardiac or respiratory arrest. Haemoptysis, rhinorrhoea, and stomatitis have been associated with inhalation of acetylcysteine.

Reviews.

1. Sandilands EA, Bateman DN. Adverse reactions associated with acetylcysteine. *Clin Toxicol* 2009; 47: 81–8.

Hypersensitivity. The most common symptoms of patients with **anaphylactoid** reactions after the intravenous use of acetylcysteine in the treatment of paracetamol poisoning are rash and pruritus; other features have included flushing, nausea or vomiting, angioedema, tachycardia, bronchospasm, hypotension, and hypertension;[1-3] ECG abnormalities associated with an anaphylactoid reaction have also been reported in a patient.[4] Anaphylactoid reactions to intravenous acetylcysteine appear to be dose-related.[5] One group estimated that when acetylcysteine was given correctly the frequency of the anaphylactoid response was between 0.3 and 3%, whereas 11 of 15 patients who had received an overdose had an anaphylactoid reaction.[6] Intradermal testing and study of plasma-acetylcysteine concentrations in patients who developed

reactions to acetylcysteine suggests a 'pseudo-allergic' rather than an immunological reaction,[7,8] although symptoms consistent with a serum sickness-like illness developed after exposure to acetylcysteine in one patient.[9] It has been suggested that generalised reactions to acetylcysteine can be treated with intravenous injection of an antihistamine;[5,10] infusion of acetylcysteine should be temporarily stopped but can usually be restarted at a slower rate without further reaction.[3] Life-threatening respiratory or cardiovascular symptoms require first-line treatment with adrenaline.

Symptoms after overdosage with acetylcysteine have been more severe. Hypotension appears to be especially prominent;[4] additional symptoms have included respiratory depression, haemolysis, disseminated intravascular coagulation, and renal failure, but some of these may have been due to paracetamol poisoning.[1] Death occurred in 3 patients who received an overdose of acetylcysteine while being treated for paracetamol poisoning,[1,11] but in 2 of them the role of acetylcysteine in this outcome was unclear.

1. Mant TGK, *et al.* Adverse reactions to acetylcysteine and effects of overdose. *BMJ* 1984; 289: 217–19.
2. Dawson AH, *et al.* Adverse reactions to N-acetylcysteine during treatment for paracetamol poisoning. *Med J Aust* 1989; 150: 329–31.
3. Pizon AF, LoVecchio F. Adverse reaction from use of intravenous N-acetylcysteine. *J Emerg Med* 2006; 31: 434–5.
4. Bonfiglio MF, *et al.* Anaphylactoid reaction to intravenous acetylcysteine associated with electrocardiographic abnormalities. *Ann Pharmacother* 1992; 26: 22–5.
5. Bailey B, McGuigan MA. Management of anaphylactoid reactions to intravenous N-acetylcysteine. *Ann Emerg Med* 1998; 31: 710–15.
6. Sunman W, *et al.* Anaphylactoid response to intravenous acetylcysteine. *Lancet* 1992; 339: 1231–2.
7. Bateman DN, *et al.* Adverse reactions to N-acetylcysteine. *Hum Toxicol* 1984; 3: 393–8.
8. Donovan JW, *et al.* Adverse reactions of N-acetylcysteine and their relation to plasma levels. *Vet Hum Toxicol* 1987; 29: 470.
9. Mohammed S, *et al.* Serum sickness-like illness associated with N-acetylcysteine therapy. *Ann Pharmacother* 1994; 28: 285.
10. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; (Dec.): 496–9.
11. Anonymous. Death after N-acetylcysteine. *Lancet* 1984; i: 1421.

Precautions

Acetylcysteine should be used with caution in asthmatic patients. It should also be used with caution in patients with a history of peptic ulcer disease, both because drug-induced nausea and vomiting may increase the risk of gastrointestinal haemorrhage in patients predisposed to the condition, and because of a theoretical risk that mucolytics may disrupt the gastric mucosal barrier. The volume of intravenous fluid required when acetylcysteine is given for the treatment of paracetamol overdosage may increase the risk of fluid overload. This may result in hyponatraemia, seizures, and death, in certain patients including children, those requiring fluid restriction, or those who weigh less than 40 kg.

Asthma. Bronchospasm precipitated in 2 asthmatic patients[1] and severe asthma and respiratory arrest in another[2] have been reported after intravenous treatment with acetylcysteine. There is also a report of a patient with brittle asthma who had a similar reaction and subsequently died after receiving intravenous treatment with acetylcysteine.[3] The increased risk does not justify delaying or witholding acetylcysteine in asthmatic patients with paracetamol poisoning, but consideration might be given to initial intravenous infusion over 30 to 60 minutes rather than the conventional 15 minutes.[4] However, a large multicentre study found no benefit from the more prolonged infusion—see Paracetamol under Poisoning and Toxicity, p. 1653.2.

1. Ho SW-C, Beilin LJ. Asthma associated with N-acetylcysteine infusion and paracetamol poisoning: report of two cases. *BMJ* 1983; 287: 876–7.
2. Reynard K, *et al.* Respiratory arrest after N-acetylcysteine for paracetamol overdose. *Lancet* 1992; 340: 675.
3. Appelboam AV, *et al.* Fatal anaphylactoid reaction to N-acetylcysteine: caution in patients with asthma. *Emerg Med J* 2002; 19: 594–5.
4. Schmidt LE, Dalhoff K. Risk factors in the development of adverse reactions to N-acetylcysteine in patients with paracetamol poisoning. *Br J Clin Pharmacol* 2001; 51: 87–91.

Hepatic impairment. The total clearance of acetylcysteine in patients with cirrhosis was found to be markedly impaired, and the elimination half-life almost twice that of healthy controls.[1] Since some of the more serious adverse effects of acetylcysteine occur when plasma concentrations are high, the authors considered that increased vigilance for untoward anaphylactoid reactions and other adverse effects was necessary in patients with cirrhosis receiving acetylcysteine, and further studies to determine the optimum dosage regimen in such patients were required.

1. Jones AL, *et al.* Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease. *Aliment Pharmacol Ther* 1997; 11: 787–91.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acetylcysteine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Acetylcysteine is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations occur about 0.5 to 1 hour after oral doses of 200 to 600 mg.[1] Some studies indicate dose-dependent pharmacokinetics with peak concentrations, the time taken to reach peak concentrations, and bioavailability increasing with increasing doses.[2] Acetylcysteine may be present in plasma as the parent compound or as various oxidised metabolites such as *N*-acetylcystine, *N,N*-diacetylcystine, and cysteine either free or bound to plasma proteins by labile disulfide bonds or as a fraction incorporated into protein peptide chains.[3] In a study about 50% was in a covalently protein-bound form 4 hours after a dose.[4] Oral bioavailability is low and mean values have ranged from 4 to 10% depending on whether total acetylcysteine or just the reduced forms are measured.[4,5] It has been suggested that acetylcysteine's low oral bioavailability may be due to metabolism in the gut wall and first-pass metabolism in the liver.[4,5] Renal clearance may account for about 30% of total body clearance.[5] On intravenous dosage mean terminal half-lives have been calculated to be 1.95 and 5.58 hours for reduced and total acetylcysteine, respectively; the terminal half-life of total acetylcysteine was 6.25 hours after oral doses.[4]

For reference to altered pharmacokinetics in patients with hepatic impairment, see above.

1. Holdiness MR. Clinical pharmacokinetics of N-acetylcysteine. *Clin Pharmacokinet* 1991; 20: 123–34.
2. Borgström L, Kågedal B. Dose dependent pharmacokinetics of N-acetylcysteine after oral dosing to man. *Biopharm Drug Dispos* 1990; 11: 131–6.
3. De Caro L, *et al.* Pharmacokinetics and bioavailability of oral acetylcysteine in healthy volunteers. *Arzneimittelforschung* 1989; 39: 383–6.
4. Olsson B, *et al.* Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. *Eur J Clin Pharmacol* 1988; 34: 77–82.
5. Borgström L, *et al.* Pharmacokinetics of N-acetylcysteine in man. *Eur J Clin Pharmacol* 1986; 31: 217–22.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: AC Lan; ACC; Acemuk; Broncolium; *Austral.*: Acetadote; Mucomyst†; Parvolex†; *Austria*: ACC; Aeromuc; Fluimucil; Husten ACC; Hustenloser; Mucobene; *Belg.*: Bronchocil; Docacetyl†; Lysomucil; Lysox; Nactop; Pectomucil; *Braz.*: Aires; Bromuc; Cisteil; Flucistein; Fluicis; Fluimucil Solucao Nasal; Fluimucil; Fluiteina; Mucocetil; NAC; *Canad.*: Mucomyst; Parvolex; *Chile*: Fluimucil; Mucolitico; *China*: Asixintai (阿思欣泰); Fluimucil (富露施); Mucosol (爱可茉); Yi Wei Shi (易维适); *Cz.*: ACC; Fluimucil; Mucobene; NAC; Solmucol; *Denm.*: Granon; Kuril; Mucolysin; Mucomyst; *Fin.*: Mucomyst; Mucoporetta†; *Fr.*: Broncoclar†; Codotussyl Expectorant; Euronac Exomuc; Fluimucil; Genac; Humex Expectorant; Mucolator†; Mucomyst; Mucomystendo; Mucospire†; Solmucol; *Ger.*: ACC†; Acemuc; Acetabs†; Acetyst†; Fluimucil; Myxofat; NAC; Tussamag NAC†; *Gr.*: Bioscal; Chriceryl; Cross; Elicor; Fluimucil; Flumil Antidoto; Flustaren; Hevox; Kantrenol; Mucomyst; Neocof; Ovoctil; Panfaco; Parvolex; Saloril; Spacyl; Trebon-N; Vaden; Vedilan-T; Vlenolys; *Hong Kong*: Exomuc; Fluimucil; Hidonac; Madame Pearl's Mucolytic; Mutamso; Parvolex†; Solmucol; *Hung.*: ACC; Fluimucil; NAC†; Solmucol; Sputopur; *India*: Cilol; Fluimucil; Flumucil; Gluton; Mucare; Mucinac; Mucohelp; Mucomelt; Mucomix; Mucosys; Mucotyle; Mucyst; Nacel; Nacfil; *Indon.*: Fluimucil; Hidonac; Mucylin; Nytex; Pectocil; Simucil; *Irl.*: Parvolex; *Israel*: Reolin; RheuNAC†; Siran; Tiran†; *Ital.*: Altersol; Brunac Fluimucil; Hidonac; Mucisol; Mucofial; Mucofrin; Mucoxan; Solmucol; Tirocular; Ultraflu; *Malaysia*: Acetin; Fluimucil; Hidonac; Mucolator; Parvolex†; *Mex.*: ACC; *Neth.*: Bisolbruis; Fluimucil; Kruidvat Hoesttabletten Acetylcysteine; Solmucol†; *Norw.*: Bronkyl; Mucomyst; *NZ*: Acetadote; Parvolex; *Philipp.*: Broncofem; Fluimucil; Hidonac; Pharcetil; Solmucol†; *Pol.*: ACC; Fluimucil; Syntemucol†; Tussicom; *Port.*: Bluval; Cetussin; Fluimucil; Flumil†; Mucolator†; Pulmosal; Tirocular; *Rus.*: ACC (АЦЦ); Exomuc (Экзомюк)†; Fluimucil (Флуимуцил); Muconex (Муконекс); NAC (Н-АЦ); *S.Afr.*: ACC; Amuco; Mucolator; Parvolex; Solmucol; *Singapore*: ACC; Codotussyl; Fluimucil; L-Cimexyl†; Parvolex†; Solmucol; Spatam; *Spain*: Fluimucil; Flumil Antidoto; Flumil; Flumonac†; Frenacil†; Iniston Mucus; Mucoaliv; Ratiomucol; *Swed.*: Viskoferm; *Switz.*: ACC; Acemucol; DemoLibral†; Dynamucil; Ecomucyl; Fluimucil toux grasse; Fluimucil; Helvetussin; Muco-Mepha; Muco-X; Mucofluid; Mucomed; Mucostop; NeoCitran Expectorant; Secresol†; Solmucol; *Thai.*: Acetin; Alistine; Cystaline; Flemex-AC; Flucil; Fluimucil; Hidonac; Mucil; Muclear; Mucocil; Mucolid; Mucolise; Mucotic; Mucoza†; Mysoven; NAC; Simucin; Stenac; *Turk.*: Act; Asist; Brunac Extal; Mentopin; Miratta; Mucolator; Muconex; Mukolatin; Mukosetil; NAC; Oxxa; *UK*: Parvolex; *Ukr.*: ACC (АЦЦ); Acestad (Ацестад); Acetal C (Ацетал С); Fluimucil (Флуимуцил); *USA*: Acetadote; Mucomyst†.

Multi-ingredient Preparations. *Arg.*: Acemuk Biotic; Acemuk L; *Braz.*: Accuvit; Rinofluimucil; *Fr.*: Rhinofluimucil; *Hong Kong*: Rinofluimucil†; *Hung.*: Rinofluimucil; *India*: D-Gard; Fourts-B; Horac; Koxcure; L-Nit; Mucomelt Forte; Mucomelt-A; Mucovent; Nefrosave; Oximet; Oxydex; *Indon.*: Dorbigot; nutrivision; Proview; Sistenol; *Irl.*: Ilube†; *Ital.*: Broncosulfur; Dicotuss; Migel; Rinofluimucil; *Philipp.*: Lungcaire Plus; *Port.*: Rinofluimucil; *Rus.*: Rinofluimucil (Ринофлуимуцил); *Singapore*: Hidonac; *Spain*: Fluimucil Complex; Rinoflumil; *Switz.*: Fluimucil Grippe Day & Night; Rinofluimucil; Solmucaine; Solmucalm; *Thai.*: Fluimucil Antibiotic†; Rinofluimucil; *UK*: Ilube; *Ukr.*: Helpex Breathe (Хелпекс Бриз); Livonorm (Ливонорм); Rinofluimucil (Ринофлуимуцил); *USA*: ALZ-NAC; Cerefolin NAC; Diabetiks; PowerMate.

Pharmacopoeial Preparations

BP 2014: Acetylcysteine Eye Drops; Acetylcysteine Injection;
USP 36: Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution; Acetylcysteine Solution.

Acetyldihydrocodeine Hydrochloride

Acetildihidrocodeína, hidrocloruro de; Ацетилдигидрокодеина Гидрохлорид.

4,5-Epoxy-3-methoxy-9a-methylmorphinan-6-yl acetate hydrochloride.

$C_{20}H_{25}NO_4$,HCl=379.9

CAS — 3861-72-1 (acetyldihydrocodeine).

ATC — R05DA12.

ATC Vet — QR05DA12.

UNII — HFF29F23AG.

Profile

Acetyldihydrocodeine hydrochloride is an opioid derivative related to dihydrocodeine (p. 52.2) that has been used as a centrally acting cough suppressant for non-productive cough (p. 1651.2) in a usual oral daily dose of 20 to 50 mg; no more than 20 mg should be taken as a single dose.

Ambroxol Hydrochloride *(BANM, rINNM)*

Ambroksolihydroklorīdi; Ambroksolio hidrochloridas; Ambroxol, Chlorhydrate d'; Ambroxol, hidrocloruro de; Ambroxol hydrochlorid; Ambroxol-hidroklorid; Ambroxolhydrochlorid; Ambroxolhydroklorid; Ambroxoli Hydrochloridum; Hidrocloruro de ambroxol; NA-872 (ambroxol); Амброксола Гидрохлорид.

trans-4-(2-Amino-3,5-dibromobenzylamino)cyclohexanol hydrochloride.

$C_{13}H_{18}Br_2N_2O$,HCl=414.6

CAS — 18683-91-5 (ambroxol); 15942-05-9 (ambroxol hydrochloride); 23828-92-4 (ambroxol hydrochloride).

ATC — R05CB06.

ATC Vet — QR05CB06.

UNII — CC995ZMV90.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Ambroxol Hydrochloride). A white or yellowish crystalline powder. Sparingly soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Protect from light.

Profile

Ambroxol is a metabolite of bromhexine (p. 1656.3) and is used similarly as a mucolytic. It has also been stated to have local anaesthetic properties. It is given in a usual oral daily dose of 60 to 120 mg of the hydrochloride in 2 divided doses. Ambroxol has also been given by inhalation, injection, or rectally. It is also available as lozenges for the symptomatic relief of sore throat.

References.

1. Schutz A, *et al.* Local anaesthetic properties of ambroxol hydrochloride lozenges in view of sore throat: clinical proof of concept. *Arzneimittelforschung* 2002; 52: 194–9.
2. Beck KM, *et al.* Antiinflammatory properties of ambroxol. *Eur J Med Res* 2008; 13: 557–62.
3. Malerba M, Ragnoli B. Ambroxol in the 21st century: pharmacological and clinical update. *Expert Opin Drug Metab Toxicol* 2008; 4: 1119–29.
4. de Mey C, *et al.* Efficacy and safety of ambroxol lozenges in the treatment of acute uncomplicated sore throat: EBM-based clinical documentation. *Arzneimittelforschung* 2008; 58: 557–68.

Adverse effects. *HYPERSENSITIVITY.* Ambroxol-induced contact dermatitis has been reported;[1,2] in one case tested, the patient was not cross-sensitive to the chemically similar bromhexine.

1. Mancuso G, Berdondini RM. Contact allergy to ambroxol. *Contact Dermatitis* 1989; 20: 154.
2. Monzón S, *et al.* Ambroxol-induced systemic contact dermatitis confirmed by positive patch test. *Allergol Immunopathol (Madr)* 2009; 37: 167–8.

Pharmacokinetics. References to pharmacokinetic studies of ambroxol.

1. Hammer R, *et al.* Speziesvergleich in Pharmakokinetik und Metabolismus von NA 872 Cl Ambroxol bei Ratte, Kaninchen, Hund und Mensch. *Arzneimittelforschung* 1978; 28: 899–903.

2. Jauch R, *et al.* Ambroxol. Untersuchungen zum Stoffwechsel beim Menschen und zum quantitativen Nachweis in biologischen Proben. *Arzneimittelforschung* 1978; 28: 904–11.
3. Vergin H, *et al.* Untersuchungen zur Pharmakokinetik und Bioäquivalenz unterscheidlicher Darreichungsformen von Ambroxol. *Arzneimittelforschung* 1985; 35: 1591–5.

Respiratory disorders. Mixed results[1-3] were obtained when ambroxol was used in chronic bronchitis or chronic obstructive pulmonary disease (COPD—p. 1199.1); in a randomised study, it was no better than placebo in preventing acute exacerbations of COPD; however, in a subset of patients with more severe disease, ambroxol therapy reduced the number of exacerbations.[4] It was ineffective[5] when given to mothers for the prophylaxis of neonatal respiratory distress syndrome (p. 1608.3), although it may be of modest benefit in the early treatment of established disease in infants.[6,7]

Inhalation of ambroxol aerosol has also produced beneficial effects in a patient with alveolar proteinosis who refused alveolar lavage.[8]

For the use of mucolytics in productive cough, see p. 1651.2.

1. Olivieri D, *et al.* Ambroxol for the prevention of chronic exacerbations: long-term multicenter trial: protective effect of ambroxol against winter semester exacerbations: a double-blind study versus placebo. *Respiration* 1987; 51 (suppl 1): 42–51.
2. Guyatt GH, *et al.* A controlled trial of ambroxol in chronic bronchitis. *Chest* 1987; 92: 618–20.
3. Alcozer G, *et al.* Prevention of chronic bronchitis exacerbations with ambroxol (Mucosolvan Retard): an open, long-term, multicenter study in 5,635 patients. *Respiration* 1989; 55 (suppl 1): 84–96.
4. Malerba M, *et al.* Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD: double-blind, randomized, multicenter, placebo-controlled study (the AMETHIST Trial). *Pulm Pharmacol Ther* 2004; 17: 27–34.
5. Dani C, *et al.* Antenatal ambroxol treatment does not prevent the respiratory distress syndrome in premature infants. *Eur J Pediatr* 1997; 156: 392–3.
6. Wauer RR, *et al.* Randomized double blind trial of Ambroxol for the treatment of respiratory distress syndrome. *Eur J Pediatr* 1992; 151: 357–63.
7. Schmalisch G, *et al.* Changes in pulmonary function in preterm infants recovering from RDS following early treatment with ambroxol: results of a randomized trial. *Pediatr Pulmonol* 1999; 27: 104–12.
8. Diaz JP, *et al.* Response to surfactant activator (ambroxol) in alveolar proteinosis. *Lancet* 1984; i: 1023.

Uricosuric action. A study[1] was carried out in 48 young male healthy subjects to examine the uricosuric effect of ambroxol. The minimum effective dose for lowering plasma-uric acid concentrations was found to be between 250 and 500 mg daily given in 2 divided doses. Although these doses are much higher than those used to treat bronchopulmonary disease, doses as high as 1 g daily were well tolerated.

1. Oosterhuis B, *et al.* Dose-dependent uricosuric effect of ambroxol. *Eur J Clin Pharmacol* 1993; 44: 237–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ambril; Antitusivo; Apracur Expectorante; Branzol; Bronquisedan Ninos; Cortos; Expectosan Novo Te Caliente; Mucosolvon; Tavinex Expectorante; Tavinex Expectotabs; Teosona Expectorante; Tosambrex; Tosedrin Jarabe; *Austria*: Ambrobene; Ambrohexal; Mucoangin; Mucosan; Mucosolvan; *Belg.*: Mucoangin; Surbronc; *Braz.*: Ambroflux; Ambrol; Ambroten†; Ambroxmel; Anabron; Broncoflux; Bronxol; Expectuss; Fluibron; Fluidin; Fluisolvan; Mucibron; Mucoangin; Mucoclean; Mucolin; Mucosolvan; Mucoxolan; Neossolvan; Spectoflux; *Chile*: Broncot; Esanflu; Fluibron; Fluomit; Mintamox; Mucosolvan; Muxol; Tocalm; *China*: Ai Mu (艾沐); Ambrohexal (安普索); Ao Gu Li (奥古丽); Bei Lai (贝莱); BiYu (必与); Bromussyl (百沫舒); En Jiu Ping (恩久平); Fei De Xing (菲得欣); Gei Xin (给欣); Hai Tian Xin (海天欣); Jinxin (津欣); Kai Shun (开顺); Kao Fu Ke (考夫克); Lansu (兰苏); Losolvan (乐舒凡); Mucosolvan (沐舒坦); NaiBang (耐邦); Nuo Jian (诺健); Pingtan (平坦); Rui Tian (瑞田); Run Jing (润津); Shu Tan Qing (抒坦清); Shuai Ke Tan (帅克坦); Shuang Chang (双偿); Tan Jing (坦静); Tan Ke Shu (坦刻抒); Wei Ke Lai (维可莱); Xin De Sheng (欣得生); Yi Nuo Shu (伊诺舒); *Cz.*: Ambex; Ambrobene; Ambrosan; Ambrospray; Dr Rentschler Hustenloser†; Flavamed; Halixol; Mucosin; Mucosolvan; Neo-Bronchol; Solvolan; *Denm.*: Flavamed; Mucoangin; *Fin.*: Flavamed; *Fr.*: Lysopadol; Muxol; Surbronc; *Ger.*: Ambrobeta; Ambrohexal†; Expit; frenopect†; Larylin Husten-Loser Pastillen†; Lindoxyl†; Mucoangin; Mucosolvan; Padiamuc†; Wick Hustenloser; *Gr.*: Abrobion; Abrolen; Afrodor; Amboral; Ambri-Xil; Ambromyc; Anavix; Apochralen; Aprinol; Auroxidol; Auroxol; Broxol; Bunafon; Celibron; Dolcevin; Ebertuss; Effercet; Erosil; Famucosolv; Fluibrox; Grenovix; Hivotex; Kriolen; Lextarol; Lisopulm; Mavixan; Mucolin; Mucosolvan; Mucovix; Nabelon; Nibren; Olbenorm; Pharmaprol; Provixen-N; Puntol; Respirol; Saribal; Stefolant; Strubelin; Tevoril; Tosse; Tussefar; Zyrantol; *Hong Kong*: Amxol; Lambroxol†; Marbroxol†; Max; Mucobrox†; Mucosolvan; Qualisolvon; *Hung.*: Ambrobene; Ambrohexal†; Halixol; Mucoangin; Solvolan†; *India*: Acocontin†; Acolyt†; Ambril; Ambrodil; Ambrolite; Amsol; Coscoril; Inhalex; Kofarest; Liquidix; Mucolite; Mucoresp; *Indon.*: Ambril; Berea; Brommer; Bronchopront; Broncozol; Broxal; Cystelis; Epexol; Extropect; Gunapect†; Interpec; Lapimuc; Limoxin; Molapect; Mucera; Mucolica; Mucopect; Mucos; Mucoxol; Nufanibrox; Promuxol; Roverton; Silopect; Sohopect†; Transbroncho; Transmuco; *Ital.*: Ambrofluid; Ambrotus; Amobronc; Atus; Broxol; Brufix; Fluibron; Fluixol; Gammaxol; Lintos; Muciclar; Mucoaricodil; Mucobront†; Mucosolvan; Secretil; Surfactal; Tauxolo; Viscomucil; Zerinol Gola; *Jpn*: Mucosal; Mucosolvan; *Malaysia*: Amtuss; Amxol; Axol; Mucosolvan; Shinoxol; Strepsils Chesty Cough; *Mex.*: Ambrofur; Amocol; Axol; Balsibron; Bicronux; Bionoxol; Boxolam†; Brogal; Bronolban; Brosolan†; Broxaquim; Broxofar; Broxoffler; Broxol; Broxolim; Cloxan; Ebromin; Euroxol; Expeflen; Ital-Ultra; Loexom; Loxibrin†; Mucibron; Mucoangin; Mucosolvan; Mucovibrol; Mucoxol; Musalten; Musvan; Oxolvan; Prospec; Protitus; Randex; Sekretovit; Septacin; Seraxol-S; Solpat; Tobrin; Trimexine; Tunitol-BX; Tusibron; Ulax-F; Viaxol; Weisal; *Neth.*: Bisolangin; Mucoangin; Rexambro; *Philipp.*: AMB; Ambroday; Ambrolex; Ambromax; Atrivex; Brocof; Bromace; Bromacef; Broxan; Broxifil; Broxil-M; Broxitrol; Broxolvan†; Bxolpen; Expel; Genox; Medibron; Mepebrox†; Mucosolin; Mucosolvan; Mucovis; Mucusurf; Myracof; Philemasol; Ponteft†; Pulmobrol; Relicof; Resbron; Sinecod Exp; Sobromer; Strepsils Chesty Cough; Sybron; Venteze; Voxoll; Zircam; Zobrixol; *Pol.*: Aflegan; Ambrol†; Ambrohexal; Ambroksol; Ambrosan; Ambrosol; Deflegmin; Entus; Flavamed; Mucoangin; Mucosolvan; Mukobron†; Tussal Expectorans; *Port.*: Benflux; Bromax; Broncoliber; Bronxol; Drenoxol; Fluidox; Fluidrenol; Hipotosse; Lactucol; Mucodrenol; Mucosolvan; Mucotosse; *Rus.*: Ambrobene (Амбробене); Ambrohexal (Амброгексал); Ambrosan (Амбросан); Ambrosol (Амбросол)†; Bronchorus (Бронхорус); Bronchowern (Бронховерн); Bronhoxol (Бронхоксол); Flavamed (Флавамед); Halixol (Халиксол); Lasolvan (Лазолван); Medovent (Медовент)†; Medox (Медокс); Neo-Bronchol (Нео-Бронхол); Suprima-Kof (Суприма-Коф); *Singapore*: Amxol; Axol; Max; Mucoclear; Mucosolvan; Shinoxol; Strepsils Chesty Cough; *Spain*: Ambrolitic†; Dinobroxol; Lizipadol; Motosol; Mucibron; Mucosan; Naxpa; *Swed.*: Mucoangin; *Switz.*: Bisolvon Ambroxol; Lysopaine dol Ambroxol; Mucabrox; Mucoangin; Mucosolvon; *Thai.*: Ambixol; Ambrocin; Ambrolex; Ambrolytic; Ambrox; Ambroxan; Ampromed; Amtuss; Amxol; Bro-Am; Broncol†; Broxol; Max†; Medovent†; Misovan; Movent; Mubroxol; Muco; Mucobrox; Mucodic; Mucolan†; Mucolax; Mucolid; Mucolyse; Mucomed; Mucopec; Mucosal; Mucosolvan; Mucovon; Mucoxine; Mucozan†; Musocan; Mybroxol; Nucobrox; Polibroxol; Secretin; Simusol; Strepsils Chesty Cough; Streptuss-AX; *Turk.*: Ambreks; Ambrol; Cofitus; Fluibron; Mukoral; Pulmor; Sekrol; Tusilin; Tusol; Tusulin; *UAE*: Mucum; *Ukr.*: Ambrobene (Амбробене); Ambrohexal (Амброгексал); Ambrosan (Амбросан); Ambrotard (Амбротард); Bronchoval (Бронховал); Flavamed (Флавамед); Lasolvan (Лазолван); Medox (Медокс); *Venez.*: Ambril; Ambromuco; Ambrox; Benflux; Brocantol; Bronchopront; Litusix; Misulvan; Mucoangin; Mucorama; Mucosolvan; Muxen; Xolvax.

Multi-ingredient Preparations. *Arg.*: Aliviatos; Amoxidal Respiratorio Duo; Amoxidal Respiratorio; Amoxigrand Bronquial; Amoxipenil Bronquial; Antitusivo L; Aseptobron Respiratorio; Bronquisedan Mucolitico; Bronquisedan; Cefaclina Bronquial; Grinsil Respiratorio Duo; Grinsil Respiratorio NF; Ideobron; Letondal; Lorabrox; Muco Dosodos Biotic; Muco Dosodos; Mucoprednibron; Mucosolvon Compositum; No-Tos Biotic; Nobactam Bronquial; Oxibron NF; Oximar Respiratorio†; Pulmonix Plus; Toraxan; Trifamox Bronquial Duo; *Austria*: Mucospas; *Chile*: Ambrotos; *China*: Ambrocol (易坦静); *Cz.*: Doxycyclin Al Comp; *Ger.*: Ambrodoxy†; Ambroxol AL comp†; Ambroxol comp; Broncho-Euphyllin; Doxy Comp†; Doxy Plus†; Spasmo-Mucosolvan; *India*: Abcet; Acolate Plus; Airitis Plus; Airtis Plus; Alcetra Plus; Aldine-D; Alkarex-PD; Alnacet-AL; Altec; Ambcet; Ambicet; Amborex-GS; Ambrex; Ambril-S; Ambril-SG; Ambro PD; Ambro S; Ambro TS; Ambrodex; Ambrodil Plus; Ambrodil-S; Ambrogen-S; Ambrol Plus; Ambrol-AM; Ambrol-C; Ambrol-GPC; Ambrol-TG; Ambrolax-PD; Ambrolax; Ambrolite-2S; Ambrolite-S; Ambrolite-ST; Ambros-GM; Ambrosin-T; Ambrosol; Ambroter; Ambrowin; Ambroxit; Amcare; Amcof; Amcold; Amgat; Amlee-P; Amox-AR; Amriz; Amrolite 2S; Amven-C; Amy; Amyrd; Arbid-A; Arcuf Plus; Arid-D; Arid; Arikof-P; Arolin-XN; Asthalin AX; Atoril; Aurox 50; Avirox-AM; Axalin Expectorant; Axalin-AX†; Axalin; Axol Plus; Axol-XL; Azintra-AX; Azithral Jun; Azro AM; Azyxin Plus; Bluetus; Borox-L; Bricarex A; Brocin; Brocoter-A; Brodil; Brofentol Plus; Bromcough; Broncodil; Broncozone; Bronq; Brox; Broxter; Calscot-AX; Canrox-A; Car-OD; Cedbrox; Ceftas AL; Ceuliv A; Cetmet TCF; Cetry Plus; Cetzine-A; Cez-A; Clamoxy A; Clear Chest; Cleded-AT; Cledex-AT; Cobury-AX; Codril-AT; Codril-P; Cofaid-EX; Coftex-AG; Coftex-DMR; Cogof-A; Coldastat-LX; Coldman; Combicold; Copeb; Corico-CS; Corid-B; Coriminic X; Corophen-A; Coscopin-BR; Cosome-A; Cosyp-E; Covil-A; Cozy-AM; Cozy-AM; Cratex; Cufdex-EX; Decofed-X; Deletus-BX; Dilevocet-Plus; Dilo-BM; DM; Dox-M-A; DYL-AX; Ecogat A; Elcet-P; Elcy-A; Elsol-S; Elsol-T; Euphomin Plus; Ex-GTM; Exituss; Exol; Exolit; Expectus; Festa; Finecef AM; Floxigat M; Fluzet X; Gatikind-AM; Gatrich; Gatus; Hlcet-AX; His-P; Historil; Idalez Plus; Indikof-B; Instaryl-P; Intacof-S; Intragat-AM; Kafban; Kazibrox; Kefdil-AX; Kevrox-SA; Kickkof; Kofarest Expectorant; Kofarest; Kofban-EX; Kofrid Plus; Koxcure; Kufgen-X; Kufnil-A; L-Cin-A; L-Triz Plus; L-Triz-A; Laveta-A; Laz-AX; Lazine Plus; LCF; LCZ-Plus; LCZ-XP; Le Zyncet-A; Lebact-AM; Lecope-AD; Leczine-A; Lenex; Lepit-A; Lepit-AM; Leverest-AM; Levocet Plus; Levogo Plus; Levoriz-AM; Levostar Plus Exp; Levostar Plus; Levostar-AM; Levotan; Levotra-A; Levzed-A; Lezo-AM; LPast-AM; LG Plus; LG-Plus; Litcoff-P; Litcoff; Livbest-AM; Lorex-AP; Lorfast-AM; Lorfast-AM; Luzer-A; Mags; Marex; Medirox-A; Microdox; Mituss-AX; Mucaryl-AX; Mucobar-S; Mucoclav; Mucomelt-A; Mucomox; Mucopen; Mucoresp Plus; Mucoresp-CT; Mucoresp-CZ; Mucoresp; Mucovent; Munorm; Muscarin; Mutech; Nam Cold-SR; NBLcet Plus; Nizla Plus; Norvent; Novamox AX; Nozik; NT-Kuf-AM; Nucope-AD; Nutuss-A; Oox-LC; Oox-P; Oox; Optex-AT; Roxeptin-ME; Suprivent-A; *Mex.*: Acimox-Ex; Aeroflux; Alerfin Ex; Alexing; Ambodil-C; Aminoefedrison; Apomuxol; Balsibron-C; Biovicam Ex; Bisincof; Brogal Compositum; Brogal-T; Brogamax; Brominol-C†; Bronar; Bronolban-M; Broquixol; Brosolan C†; Broxofar Compuesto; Broxol Air; Broxol Plus; Broxolim-C; Brumax; Cefabroxil; Cibronal; Cobadex; Connex; Coricidin Expec; Dexbrolex; Dexol; Dexoltryn; Dinolan; Dizolvin-Flux; Dofaxil; Doralan-Ax; Ebromin P; Paribrox; Perlex; Flamebin; Fludexol-CL; Fluvicil; Fluxibit; Fluxol; Fultac; Gelamxol; Gimabrol†; Histiacil NF; Laritol Ex; Linfarden; Loexom FC; Loexom FS; Loxorol; Mucoflux; Mucosolvan Compositum; Mucovibrol Amoxi; Mucovibrol C; Musaldox; Neumyn-AS; Pentibroxil; Plexus; Ravotaf; Removil; Rezplen; Rombox; Salamflux; Sekretovit Amoxi; Sekretovit Ex; Sensibit XP; Septacin Amoxi; Septacin Ex; Seraxol; Serbol; Sermoxol; Sibilex; Solbotex; Solcibrol; Tadinar-C; Tavexyl; Tesalon Tenalif; Tesofan Ex; TheraFlu Tenalif; Torva; Toxol; Ulax-C; Vanmoxol†; *Port.*: Clembroxol; Mucospas; Ventoliber; *Rus.*: Codelac Broncho (Коделак Бронхо); Codelac Broncho with Thymus Serpyllum (Коделак Бронхо с Чабрецом Обусловлено); Coldact Broncho (Колдакт Бронхо); Rinicold-Broncho (Риникольд Бронхо); *Ukr.*: Coldact Broncho (Колдакт Бронхо)†; Helpex Breathe (Хелпекс Брез); Militan Cough (Мілітан Кашлю); Militan Cough Hot Tea (Мілітан Гарячий Чай Від Кашлю); Pectolvan C (Пектолван Ц); Pulmolor (Пульмолор); Salbroxol (Сальброксол); *Venez.*: Aeroflux; Ambroclar; Ambromuco Compositum; Arbixil; Clenbuxol; Litusix Compositum; Mucolin; Mucosolvan Compositum.

Amidefrine Mesilate *(BANM, rINN)* ⊗

5190; Amidefrina, mesilato de; Amidéfrine, Mésilate d'; Amidefrini Mesilas; Amidephrine Mesylate (USAN); Amidephrine Mesylate; Mesilato de amidefrina; MJ-5190; Амидефрина Мезилат.

3-(1-Hydroxy-2-methylaminoethyl)methanesulphonanilide methanesulphonate.

$C_{10}H_{16}N_2O_3S.CH_4O_3S$=340.4

CAS — 3354-67-4 (amidefrine); 1421-68-7 (amidefrine mesilate).

UNII — S3IG39T948.

Profile

Amidefrine mesilate is a sympathomimetic with alpha-adrenergic activity similar to that of phenylephrine (p. 1672.2). It is used for its vasoconstrictor properties in the local treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Fentrinol.

Ammonium Acetate

Amonio, acetato de; Amonowy octan; Ацетат Аммония; Уксуснокислый Аммоний.

$CH_3CO_2NH_4$=77.08

CAS — 631-61-8 (ammonium acetate); 8013-61-4 (ammonium acetate solution).

UNII — RRE756S6Q2.

Pharmacopoeias. *Br.* includes Strong Ammonium Acetate Solution.

Ammonium Bicarbonate *(BAN)*

Ammonii hydrogenocarbonas; Ammonium, bicarbonate d'; Ammónium-hidrogén-karbonát; Ammoniumvätekarbonat; Ammoniumvetykarbonaatti; Amonio, bicarbonato de; Amonio-vandenilio karbonatas; E503; Hydrogenuhličitan amonný; Бикарбонат Аммония; Гидрокарбонат Аммония; Двууглекислый Аммоний.

Ammonium hydrogen carbonate.

NH_4HCO_3=79.06.

CAS — 1066-33-7.

UNII — 4SJP434SC9.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Ammonium Hydrogen Carbonate; Ammonium Bicarbonate BP 2014). A fine, white or almost white, slightly hygroscopic, crystalline powder or white or almost white crystals. It volatilises rapidly at 60 degrees; volatilisation takes place slowly at ambient temperatures if slightly moist. It is in a state of equilibrium with ammonium carbamate. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

The BP 2014 directs that when Ammonium Carbonate is prescribed or demanded Ammonium Bicarbonate shall be dispensed or supplied.

Ammonium Carbonate

Amonio, carbonato de; Amonowy węglan; Carbonato de Amonio; E503; Карбонат Аммония; Углекислый Аммоний.
CAS — 8000-73-5.
UNII — NU5VT0FKLJ.

Pharmacopoeias. In *Fr.* Also in *USNF.*

USNF 31: (Ammonium Carbonate). A white powder, or hard, white or translucent masses having a strong odour of ammonia, without empyreuma. It consists of ammonium bicarbonate and ammonium carbamate, in varying proportions. It yields 30 to 34% of NH_3. On exposure to air it loses ammonia and carbon dioxide, becoming opaque, and is finally converted into friable porous lumps or a white powder of ammonium bicarbonate. Soluble 1 in 4 of water. It is decomposed by hot water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 30 degrees. Protect from light.

NOTE. The BP 2014 directs that Ammonium Bicarbonate shall be dispensed or supplied when Ammonium Carbonate is prescribed or demanded.

Ammonium Chloride

510; Ammonii chloridum; Ammonium Chloratum; Ammonium, chlorure d'; Ammoniumchlorid; Ammónium-klorid; Ammoniumklorid; Ammoniumkloridi; Amonio cloridas; Amonio, cloruro de; Amonowy chlorek; Chlorid amonný; Cloruro de Amonio; Muriate of Ammonia; Sal Ammoniac; Хлорид Аммония; Хлористый Аммоний.
NH_4Cl=53.49
CAS — 12125-02-9.
ATC — B05XA04; G04BA01.
ATC Vet — QB05XA04; QG04BA01.
UNII — 01Q9PC255D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *US*, and *Viet.*

Ph. Eur. 8: (Ammonium Chloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water.

USP 36: (Ammonium Chloride). Colourless crystals or white, fine or course, crystalline powder. Is somewhat hygroscopic. Freely soluble in water and in glycerol, and even more so in boiling water; sparingly soluble in alcohol. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers.

Uses and Administration

Ammonium chloride is used as an expectorant in productive cough (p. 1651.2). Other ammonium salts that have been used similarly include the acetate, bicarbonate, camphorate, carbonate, citrate (p. 2441.3), and glycyrrhizate (p. 2520.3).

Giving ammonium chloride produces a transient diuresis and acidosis. It may be used in the treatment of severe metabolic alkalosis (p. 1775.3). Each g of ammonium chloride represents 18.69 mmol of chloride. It is usually given as a 1 to 2% solution by slow intravenous infusion, in a dosage depending on the severity of the alkalosis. A concentrated solution of ammonium chloride may be diluted by sodium chloride injection.

Ammonium chloride may also be used to maintain the urine at an acid pH in the treatment of some urinary-tract disorders. It is usually given orally, often as enteric-coated tablets, in a dose of 1 to 2 g every four to six hours. Higher doses were sometimes used in forced acid diuresis procedures to aid the excretion of basic drugs, such as amfetamines, in severe cases of overdosage (but see p. 2320.1).

Ammonium chloride has been promoted for self administration as a diuretic, for example in premenstrual water retention; an oral dose of 650 mg three times daily for up to 6 days has been suggested, but such use is generally considered inappropriate.

Adverse Effects and Treatment

Ammonium salts are irritant to the gastric mucosa and may produce nausea and vomiting particularly in large doses. Large doses of ammonium chloride may cause a profound acidosis and hypokalaemia which should be treated symptomatically. Intravenous ammonium chloride can cause pain and irritation at the site of injection, which may be decreased by slowing the rate of infusion.

Excessive doses of ammonium salts, particularly if given by rapid intravenous injection, may give rise to hepatic encephalopathy due to the inability of the liver to convert the increased load of ammonium ions to urea.

Precautions

Ammonium salts are contra-indicated in patients with hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ammonium chloride as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Ammonium chloride is absorbed from the gastrointestinal tract. The ammonium ion is converted into urea in the liver; the anion thus liberated into the blood and extracellular fluid causes a metabolic acidosis and decreases the pH of the urine; this is followed by transient diuresis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Nyal Bronchitis Cough; *Ger.*: Extin N; *Singapore*: Lin So Peppermint Cough.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Austria*: Cranagil; Tonsan chronisch; *Canad.*: Nareel†; *Chile*: Rinoplex; *Fr.*: Vinicard†; *Ger.*: Muco-cyl L Ho-Len-Complex; *Hung.*: Naso-Heel S; *Switz.*: Regenaplex Nr 28b; Regenaplex Nr. 79.

Pharmacopoeial Preparations
BP 2014: Ammonium Chloride Mixture; Aromatic Ammonia Solution; Aromatic Ammonia Spirit; Strong Ammonium Acetate Solution; White Liniment;
USP 36: Ammonium Chloride Delayed-release Tablets; Ammonium Chloride Injection; Aromatic Ammonia Spirit; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution.

Benproperine *(rINN)*

ASA-158/5 (benproperine phosphate); Benproperiini; Benproperin; Benproperina; Benpropérine; Benproperinum; Бенпроперин.
1-[2-(2-Benzylphenoxy)-1-methylethyl]piperidine.
$C_{21}H_{27}NO$=309.5
CAS — 2156-27-6.
ATC — R05DB02.
ATC Vet — QR05DB02.
UNII — 3AA6IZ48YK.

Pharmacopoeias. *Chin.* includes the phosphate.

Profile

Benproperine is used as a cough suppressant in non-productive cough (p. 1651.2). It is reported to have a peripheral and central action and has been given in usual oral doses of 25 to 50 mg two to four times daily as the phosphate. Benproperine embonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fa Si Te (法思特); Fu Song (服松); Ke Pai Ning (咳哌宁); Ke Te (科特); KeLiTing (可立停); Pai Xin (哌欣); Shan Qing (山清); *Ger.*: Tussafug; *Hong Kong*: Cofrel; *Jpn*: Flaveric.

Benzonatate *(BAN, rINN)*

Bensonatat; Bentsonataatt; Benzonatato; Benzonatatum; Benzononatine; KM-65; Бензонатат.
3,6,9,12,15,18,21,24,27-Nonaoxaoctacosyl 4-butylaminobenzoate.
$C_{13}H_{18}NO_2(OCH_2CH_2)_nOCH_3$, where *n* has an average value of 8.
CAS — 104-31-4 (where n = 8).
ATC — R05DB01.
ATC Vet — QR05DB01.
UNII — 5P4DHS6ENR.

Pharmacopoeias. In *US.*

USP 36: (Benzonatate). A clear, pale yellow, viscous liquid having a faint characteristic odour. Soluble 1 in less than 1 of water, of alcohol, of chloroform, and of ether; freely soluble in benzene. Store in airtight containers. Protect from light.

Uses and Administration

Benzonatate is a cough suppressant used in non-productive cough (p. 1651.2); it is stated to act peripherally. It is related to tetracaine (p. 1996.3) and has a local anaesthetic action on mucosa. It is given to adults and children over the age of 10 years in an oral dose of 100 or 150 mg three times daily; up to 600 mg daily in divided doses may be given if necessary. Benzonatate is reported to act within about 20 minutes and its effects are reported to last for 3 to 8 hours.

Administration in children. For doses of benzonatate in children, see Uses and Administration, above.

Adverse Effects

Headache, dizziness, sedation, confusion, and visual hallucinations have been reported with benzonatate use. Other adverse effects include gastrointestinal disturbances, nasal congestion, an ocular burning sensation, pruritus, and rashes. Local anaesthetic properties can produce numbness of the mouth, tongue, and pharynx if oral preparations are chewed or sucked instead of being swallowed whole. Hypersensitivity reactions, possibly related to local anaesthesia, have included bronchospasm, laryngospasm, and cardiovascular collapse. CNS stimulation and convulsions, followed by CNS depression, may occur in overdosage; cardiac arrhythmias have also been recorded.

Overdosage. A review[1] of 2172 cases of benzonatate toxicity found moderate or major effects reported in 116 (5%). Cardiac and CNS effects were most frequently reported, including tachycardia, ventricular arrhythmia, cardiac arrest, asystole, hypotension, agitation, seizures, and coma. This included 4 deaths due to dysrhythmias. Based on 676 cases, the authors suggested that an oral dose of 200 mg or more has the potential to cause serious adverse effects in children less than 6 years old. The FDA[2] has warned that in children less than 10 years of age, signs and symptoms of overdosage can occur within 15 to 20 minutes, and that deaths have been reported within hours of accidental benzonatate ingestion.

1. Winter ML, *et al.* Benzonatate ingestion reported to the National Poison Center Database System (NPDS). *J Med Toxicol* 2010; 6: 398–402.
2. FDA. FDA drug safety communication: death resulting from overdose after accidental ingestion of Tessalon (benzonatate) by children under 10 years of age (issued 14/12/10). Available at: http://www.fda.gov/Drugs/DrugSafety/ucm236651.htm (accessed 20/12/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Benz; *Mex.*: Beknol; Benzonal; Bronpax†; Capsicof; D-Tato; Lemtosid†; Nafatosin; Novapsyl; Pebegal; Pharben; Supracof; Tesalon; Tesopen†; Texoven; Tusical†; Tusitato; Tuzzil; Velpro; *USA*: Tessalon; Zonatuss.

Pharmacopoeial Preparations
USP 36: Benzonatate Capsules.

Bibenzonium Bromide *(BAN, rINN)*

Bibenzonii Bromidum; Bibenzonio, bromuro de; Bibenzonium, Bromure de; Bromuro de bibenzonio; Diphenetholine Bromide; ES-132; Бибензония Бромид.
[2-(1,2-Diphenylethoxy)ethyl]trimethylammonium bromide.
$C_{19}H_{26}BrNO$=364.3
CAS — 59866-76-1 (bibenzonium); 15585-70-3 (bibenzonium bromide).
ATC — R05DB12.
ATC Vet — QR05DB12.
UNII — 4455J9277Q.

Profile

Bibenzonium bromide is a cough suppressant used in non-productive cough (p. 1651.2) which is stated to have a central action; it has been given orally.

Bromhexine *(BAN, rINN)*

Bromexina; Bromhexin; Bromhexina; Bromhexinum; Bromiheksiini; Butamirat; Бромгексин.
2-Amino-3,5-dibromobenzyl(cyclohexyl)methylamine.
$C_{14}H_{20}Br_2N_2$=376.1
CAS — 3572-43-8.
ATC — R05CB02.
ATC Vet — QR05CB02.
UNII — Q1J152VB1P.

Bromhexine Hydrochloride

(BANM, USAN, rINNM)

Bromheksino hidrochloridas; Bromhexina, hidrocloruro de; Bromhexine, chlorhydrate de; Brómhexin-hidroklorid; Bromhexinhydrochlorid; Bromhexin-hydrochlorid; Bromhexinhydroklorid; Bromhexini hydrochloridum; Bromiheksiinihydrokloridi; Bromoheksyny chlorowodorek; Cloridrato de Bromexina; Hidrocloruro de bromhexina; NA-274; Бромгексина Гидрохлорид.

$C_{14}H_{20}Br_2N_2,HCl$=412.6
CAS — 611-75-6.
ATC — R05CB02.
ATC Vet — QR05CB02.
UNII — YC2ZOM3Z8V.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Bromhexine Hydrochloride). A white or almost white crystalline powder. It exhibits polymorphism. Very slightly soluble in water; slightly soluble in alcohol and in dichloromethane. Protect from light.

Uses and Administration

Bromhexine is a mucolytic used in the treatment of respiratory disorders associated with productive cough (p. 1651.2). Bromhexine is usually given orally in a dose of 8 to 16 mg of the hydrochloride three times daily. It has also been given by deep intramuscular or slow intravenous injection or inhaled as an aerosol solution.

Bromhexine has also been used orally and topically in the treatment of dry eye syndromes associated with abnormal mucus production (see below).

Dry eye. Bromhexine has been used orally in the treatment of dry eye (p. 2190.1) in Sjögren's syndrome but results have been conflicting; it appears to have no effect on tear secretion in healthy subjects.[1] It has also been tried topically.

1. Avisar R, *et al.* Oral bromhexine has no effect on tear secretion in healthy subjects. *Ann Pharmacother* 1996; 30: 1498.

Respiratory-tract infection. *USE WITH AN ANTIBACTERIAL.* Bromhexine has been shown to enhance the penetration of erythromycin into bronchial secretions.[1] Although bromhexine is used as an adjuvant in the treatment of respiratory infections, few controlled studies appear to have been conducted to determine if any additional benefit is obtained. However, some studies have found improved responses with cefalexin[2] and amoxicillin.[3]

1. Bergogne-Berezin E, *et al.* Etude de l'influence d'un agent mucolytique (bromhexine) sur le passage de l'érythromycine dans les sécrétions bronchiques. *Therapie* 1979; 34: 705–11.
2. Boraldi F, Palmieri B. Antibiotic and mucolytic therapy in elderly patients with different cases of bronchopulmonary diseases. *Curr Ther Res* 1983; 33: 686–91.
3. Roa CC, Dantes RB. Clinical effectiveness of a combination of bromhexine and amoxicillin in lower respiratory tract infection: a randomized controlled trial. *Arzneimittelforschung* 1995; 45: 267–72.

Adverse Effects

Gastrointestinal adverse effects may occur occasionally with bromhexine and a transient rise in serum aminotransferase values has been reported. Other reported adverse effects include headache, dizziness, sweating, and skin rashes. Inhalation of bromhexine has occasionally produced cough or bronchospasm in susceptible subjects.

Precautions

Since mucolytics may disrupt the gastric mucosal barrier bromhexine should be used with care in patients with a history of peptic ulcer disease. Care is also advisable in asthmatic patients. Clearance of bromhexine or its metabolites may be reduced in patients with severe hepatic or renal impairment.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies bromhexine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract; peak plasma concentrations occur after about 1 hour. Bromhexine undergoes extensive first-pass metabolism in the liver: its oral bioavailability is stated to be only about 20%. It is widely distributed to body tissues. About 85 to 90% of a dose is excreted in the urine mainly as metabolites. Ambroxol (p. 1654.3) is a metabolite of bromhexine. Bromhexine is highly bound to plasma proteins. It has a terminal elimination half-life of 13 to 40 hours. Bromhexine crosses the blood-brain barrier and small amounts cross the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Amiorel; Aseptobron Expectorante; Balsasulf; Bisolvon; Bromexidril; Bromhetos; Broncocalmine; Brondilax; Bronquisedan Max; Bronquisedan Pediatrico; Catarrosine; Expectosan Extra Forte; Fadatos NF; Funciobron B; Lisi-Tos; Lorbi-Bis; Lorbi; Medex; Namir; Nastizol Expectorante; No-Tos Mucolitico; Pulmonix; Pulmosan; Qura Plus; Sandival†; Toscalmin; Tostop; ***Austral.***: Bisolvon Chesty; Duro-Tuss Chesty Cough; Duro-Tuss Mucolytic Cough Liquid†; ***Austria***: Bisolvon; ***Belg.***: Bisolvon; Bromex; Bronchi-Mereprine†; ***Braz.***: Bisolphar; Bisolvon; Bispect; Bisuran; Bronxina; ***Chile***: Bisolvon; Bropavol; Flumed†; Noremine; ***China***: Ao Qun (傲群); Fei Li Xing (菲力星); Fu Zhi (伏枝); HeKeDiSi (赫克迪思); Ka Bei (卡贝); Pu Ni Ke Si (普尼克斯); Sai Wei (赛维); ***Cz.***: Mucohex†; Paxirasol; ***Denm.***: Bisolvon; ***Fin.***: Bisolvon; Medipekt; Mucovin; ***Fr.***: Bisolvon; ***Ger.***: Bisolvon; ***Gr.***: Bisolvon; Bolisegna; Bromiramin; Bron-Hal; Bronchotussine; Butilen; Diamelitus; Neo-Pulmolysine; Seltak; ***Hong Kong***: Bisofan; Bromoson; Bromxine; Duro-Tuss Mucolytic; Ekxine; Exolit†; Extovon†; Hosolvon†; Uni-Hexine†; Vasican; ***Hung.***: Paxirasol; ***India***: Bisolvon; Bromex; ***Indon.***: Bisolvon; Bromika; Dexolut; Ethisolvan; Exovon†; Farmavon; Hexon; Hustab P; Lexavon; Mucobron; Mucohexin; Mucosolvan; Poncosolvon; Solvinex; Thephidron; Yavon; ***Irl.***: Bisolvon; ***Israel***: Movex; Mucoless; Solvex; ***Ital.***: Bisolvon; ***Jpn***: Bisolvon; ***Malaysia***: Beacolytic; Bislan; Bromxine; Disol†; Mucolex; Mucolix; Mucoxin; Vasican; ***Mex.***: Bisolvon; Bromicof; Fluexin; Meroxan†; Nastizol Ex; Normoflex; Tesacof; Toridran-N; ***Neth.***: Bisolvon; Darolan Slijmoplossende†; Kruidvat Hoestdrank Broomhexine; Kruidvat Hoestelixer†; Kruidvat Hoesttabletten Broomhexine; Otrivin; Trekpleister Hoesttabletten; ***Norw.***: Bisolvon; ***NZ***: Bisolvon; Duro-Tuss Chesty Cough; ***Philipp.***: Bidocsol; Bisolvex; Bisolvon; Broxol; Dur-Elix†; Easepex†; Extruss; Fleminate; Mucolyptus; Muconix; Mucosform; Xinebrom; ***Pol.***: Flegamina; ***Port.***: Basiflux; Bisolvon; Bromocal†; Broncoral; Lisomucin; Tosseque; ***Rus.***: Flegamin (Флегамин)†; Solvin (Солвин); ***S.Afr.***: Bisolvon; Bronkese†; ***Singapore***: Asthmaxine; Bislan; Bisolvon†; Bromxine; Duro-Tuss Chesty Cough; Duro-Tuss Chesty Cough; Exolit; Hosolvon; Mucolix; Mucosol; Vasican; ***Spain***: Bisolmed; Bisolvon; ***Swed.***: Bisolvon; Bromhex; ***Switz.***: Bisolvon; ***Thai.***: Asovon; Axistal; Belen; Bioxine; Bisoltab; Bisolvon; Bomexin†; Bromcolex; Bromex; Bromhex; Bromoson; Bromso; Bromtussin; Bromxin; Bromxine; Bronclear; Bronkase; Bronmucon; Brovol; Buzetin; Cohexine; Disol; Dutross; Extovon; Ida; Jimax; Manovon; Mihexine†; Mucine; Mucocin; Mucola; Mucopac; Mucoxin†; Musovon; Ohexine; Romulin; St Luke's Cough; Tromadil†; Usovan; ***Turk.***: Bromek; Bromeksin; Viscol; ***UAE***: Mucolyte; ***Venez.***: Bedena; Bexilon; Bisectron; Bisolvon; Bromedrina; Bromexol; Bromox; Inquixol; Kecnitril; Lisomucin; Mucobrol; Reosil; Teraflem.

Multi-ingredient Preparations. *Arg.*: Agrip; Amiorel Compuesto; Amox-G Bronquial; Amoxidal Respiratorio; Amplibenzatin Bronquial; Aseptobron Bromexina; Bio Grip Classic; Bisolvon Compositum; Cofron; Cor-Tagrip; Coris Grip; Dosulfin Bronquial; Duflegrip; Eritrobron; Espectocural; Factor Antigripal; Farintos; Finagrip Forte; Frenotos Muc; Grinsil Respiratorio; Gripaben; Matrix Grip†; Nastizol Compositum; Neumobacticel; Nexogrip; No-Tos NF; Notozen†; Panotos NF; Panotos; Paracetamol Grip NF; Pectoral Hebert; Piritos; Pulmocler; Pulmonix Grip; Qura; Refrianex Compuesto; Refrianex; Rupediol; Selectus FN; Selectus; Termogrip; Toxam; Toxambay; ***Austral.***: Benadryl Chesty Forte; Bisolvon Sinus†; Chemists Own Chesty Cough; Chemists Own Chesty Mucus Cough; Dimetapp Chesty Cough; Duro-Tuss Chesty Cough Forte; Duro-Tuss Chesty Cough Plus Nasal Decongestant; Duro-Tuss Expectorant; Duro-Tuss Sinus†; Robitussin Chesty Cough Forte; Tussinol Expectorant†; ***Braz.***: Broncatar; Bronco-Polimoxil; ***Chile***: Bauxol; Brontal; Diadicon; Esantuss; Mucobrol; Plus-Tos; ***China***: An Bu (安卜); Bi Li (毕利); Cha Xin Na Min (茶新那敏); Pu Kuai (浦快); Xi Meng (熙蒙); Xiaoke (消刻); Zheng Da Su Ke (正大素克); ***Cz.***: Bronchosan†; ***Hong Kong***: America†; Barlodin†; Bromcolin†; Bronco-DM†; Broncodin†; Cofetal†; Coltalin-GP Extra; Coughlin†; Decaugh II†; DF Multi-Symptom†; Duro-Tuss Expectorant; Fastolin†; Fusta†; Futalin†; Futara†; Mecostop†; Methor-Co†; Metoplex; Nosbrom†; Robitussin ME; Vida Cough†; Vidatapp Forte†; ***Hung.***: Nasopax; ***India***: Adcold-BR; Adcold-SBG; Aeromox; Albutamol; Alemyl-B; Alerpect; Alpha-Zedex; Ambitus; Amexine; Anacuf; Ascodex Plus; Ascodryl; Ascoril Expectorant; Ascoril; Asi-Ril; Asma-ZED; Asmatide-BR; Asmotone Plus; Ast-Ex; Asthakind; Asthavent-BR; Asthos; Atus-D; Benituss; Benylin E; Bex; Blast; Brachy; Brex-S; Brex; Brex; Bro-Zedex; Brofentol; Bromolin; Bronchosolvin; Broncorex; Bronkex; Bronkosyrup-EX; Bronmix; Bronsim; Browin Junior; Browin-TG; Brozeet; C-Cold; Capex-Bron Exp; Carecof; CC-Koff; Cefel-B; Celar; Cep-Bro; Chescare; Cheston DT; Cheston Exp; Cheston; Cinkof; Cleartuss-D; Cleartuss-T; Cof Q; Cof QX; Cofal; Cofdex Forte; Cofdex-P; Cofdex; Cofpet-DX; Cofsym; Coftex-BT; Cofvyn; Cor-4; Corinite; Cos-P; Coscoril; Cosome Exp; Cufokin; DCol-BR; Deletus P; Dolar; Dr Koff; Eascof Exp; Eascof; Edomox-B; Efelin-X; Efelin; Eledyl; Elite-P; Elkof; Elkuf; Eltocin-BR; Ep-Koff; Ero-B; Esma-PD; Estharil Plus; Eto-Salbetol; Etoxin-B Exp; Etoxin-B; Exiplon-BR; Expect-T; Flemnil; Flu-4-BR; Flu-4; Gocold; Grilinctus-BM; Hanex; Heximox; Himox-B; Ingahist-X; Ingahist; Instaryl; Intenoal; Kazibrox-BT; Kno-OL; Kofend-X; Kofkul; Koforil; Kofryl-P; Kuff-Q; Kuff-Q; Kuff-X; Kufkair; Kufnil-A; Labocof; Lamoxy-BX; Lemo Linctus; Lemohist-BG; Libitus Plus; Medkof; Megaril; Megatuss-P; Mexol-G; Mituss-BR; Monamox-BR; Moxbro; Moxind BR; Muco Asthalin; Mucoline; Mucomelt-XP; Mucorid; Mucosol; Mulitmix; Multimix; Mycocin; Neorex; New Zephrol; Nomorcuf; NSI-Ril; NT-Kuf-M; Nutuss-BR; Okaril Plus; Okaril; Otymox; Oxybro; Pulmo-Rest Expectorant†; Pulmo-Rest; Respimox; Sedosolvin; Siokof-P; Solvin; Suprivent; Terpect; Terpect; Terphylate; Toscof; Tuspel Plus; Zedex-P; Zedex; Zeecof; Zeet; Zeet; ***Indon.***: Bisolvon Extra; Bisolvon Flu; Bodrex Flu & Batuk Berdahak; Bodrexin Flu & Batuk; Brolexan†; Fortusin; Halmezin; Hustab; Mucotussan†; Nufadipect; Oskadon Flu & Batuk Berdahak; Woods' Peppermint Expectorant; ***Irl.***: Alupent Expectorant†; ***Ital.***: Tauglicolo; ***Malaysia***: Duro-Tuss Expectorant; Duro-Tuss Sinus†; Hosolvan DM; ***Mex.***: Acroxil-C; Ambrexin†; Amoxibron; Arlexen B; Berosolvon; Bisolpect Ex; Bisolvon A; Bisolvon E; Bremoxiral; Bromel†; Bromixen; Bromoxil; Brupen Compuesto; Ceclordox; Cepobrom; Duracef Expec; Eriwest; Fasinat; Fluxedan; Hidramox-M; Kodel; Lumoxbron S; Mucocef; Mucoxina; Pantobron; Penamox M; Penbritin Ex; Pentibrom; Penrexyl Expec; Quimobrom; ***NZ***: Benadryl Chesty Forte; Duro-Tuss Expectorant; Robitussin ME; ***Philipp.***: Bisolpect; Mucosform; Pecof; ***Pol.***: Flegatussin†; ***Rus.***: Ascoril Expectorant (Аскорил Экспекторант); Bronchosan (Бронхосан); Jocet (Джосет); Kasnol (Кашнол); Zedex (Зедекс)†; ***S.Afr.***: Adco-Linctopent; Benylin Chesty; Bisolvon Linctus DA; Bronkese Compound; Duro-Tuss†; Flemeze; ***Singapore***: Duro-Tuss Expectorant; Robitussin ME; SP-Brom; ***Spain***: Bactopumon; Balsoprim; Bisolvon Compositum†; Bronco Asepsilex Fuerte†; Bronco Tonic†; Bronquidiazina CR; Clamoxyl Mucolitico; Pulmo Borbalan†; ***Swed.***: Mollipect; ***Thai.***: Bisolvon EX; Bromso-Ex; Bromsuno; Bronchoprex Expectorant; Dexbroxine; Dutross-P; Ida-D; Kupa; Mucolate; Nasorest Expectorant; Pabron Cough; Presco; Robitussin ME; Tauglicolo; Tusno; ***Ukr.***: Ascoril Expectorant (Аскорил Экспекторант)†; Bro-Zedex (Бро-Зедекс)†; Bronchosan (Бронхосан)†; Helpex Anticold Syrup (Хелпекс Антихолд Сироп); Joset (Джосет); Zedex (Зедекс); ***Venez.***: Broxodin; Opilina Compuesta; Oxolavin Compuesto; Tolmex.

Brovanexine Hydrochloride *(rINNM)*

Brovanexina, hidrocloruro de; Brovanexine, Chlorhydrate de; Brovanexini Hydrochloridum; Hidrocloruro de brovanexina; Броваксина Гидрохлорид.

4-(Acetyloxy)-*N*-[2,4-dibromo-6-[(cyclohexylmethylamino)methyl]phenyl]-3-methoxybenzamide monohydrochloride.

$C_{24}H_{29}Br_2ClN_2O_4$=604.8

CAS — 54340-61-3 (brovanexine); 54340-60-2 (brovanexine hydrochloride).

UNII — 5114IS0SMG.

Profile

Brovanexine is a derivative of bromhexine (p. 1656.3) and is given orally as the hydrochloride, usually as an adjunct to antibacterials in preparations for the treatment of respiratory-tract infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Bronquimucil†; ***Spain***: Broncimucil.

Multi-ingredient Preparations. *Arg.*: Trifamox Bronquial.

Butamirate Citrate *(BANM, USAN, rINNM)*

Abbott-36581; Butamirát-citrát; Butamirate, Citrate de; Butamirati Citras; Butamirato, citrato de; Butamyrate Citrate; Citrato de butamirato; HH-197; Бутамирата Цитрат.

2-(2-Diethylaminoethoxy)ethyl 2-phenylbutyrate dihydrogen citrate.

$C_{18}H_{29}NO_3,C_6H_8O_7$=499.6

CAS — 18109-80-3 (butamirate); 18109-81-4 (butamirate citrate).

ATC — R05DB13.

ATC Vet — QR05DB13.

UNII — 67HPS1L98R.

Profile

Butamirate citrate is a cough suppressant used in non-productive cough (p. 1651.2) and stated to have a central action. The usual oral dose is up to 30 mg daily in 3 or 4 divided doses; some countries permit up to 90 mg daily in divided doses. Modified-release tablets containing 50 mg have been given 2 or 3 times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dosodos; Proking NF; Talasa NF; Tossec; ***Belg.***: Sinecod; ***Cz.***: Sinecod; Tussin; ***Gr.***: Antis; Antitoss; Bartil; Betavix; Boutavixal; Bronchofyl; Butacodin; Butagan; Butamir; Butrin; Buvastin; Chemisolv; Chributan; Codexine-R; Codimin; Devix; Doctamine; Drosten; Ellisek-S; Gertotus; Leogumil; Lotrecin; Mebronol; Minatuss; Nontoss; Novamir; Oaxen; Pandigal; Pintal; Roctylan; Rondover; Safarol; Sinecod; Siroflex; Stilex; Velkacet; Verocod; Vilvom; Zeleven; Zetapron; ***Hung.***: NeoCitran Antitussive†; Sinecod; ***Ital.***: Butiran; Lenistar†; Lexosedin; Sinecod Tosse Sedativo; ***Neth.***: Sinecod; ***Philipp.***: Sinecod; ***Pol.***: Sinecod; Supremin; ***Port.***: Sinecod; ***Rus.***: Omnitus (Омнитус); Panatus (Панатус); Sinecod (Синекод); ***Switz.***: DemoTussol; NeoCitran Antitussif; Sinecod;

Thal.: Sinecod; *Turk.*: Butamcod; Butirol; Kreval; Sinecod; Solmirat; Tusamol; Tussia.

Multi-ingredient Preparations. *Arg.*: Muco Dosodos; *Cz.*: Stoptussin; *Rus.*: Stoptussin (Стоптуссин); *Switz.*: Hicoseen†; *Ukr.*: Pectolvan Stop (Пектолван Стоп); Stoptussin (Стоптуссин).

Butetamate Citrate *(BANM, rINNM)*

Butétamate Citrate de; Butetamati Citras; Butetamato, citrato de; Butethamate Citrate; Butethamate Dihydrogen Citrate; Citrato de butetamato; Бутетамата Цитрат.

2-Diethylaminoethyl 2-phenylbutyrate citrate.

$C_{16}H_{25}NO_2.C_6H_8O_7$=455.5

CAS — 14007-64-8 (butetamate); 13900-12-4 (butetamate citrate).

UNII — 70430R0X79.

Profile

Butetamate citrate is reported to be an antispasmodic and bronchodilator and has been used alone or in combination preparations for the symptomatic treatment of coughs and other associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Heliphenicol.

Multi-ingredient Preparations. *Arg.*: Apracur Antigripal; Bio Grip 4; Bronquisedan; Febrigrip; Fugafebril; Kiper; Matrix Grip Antigripal; Mejoral Grip; Mucoprednibron; No-Tos NF; Piritos; Pulmocler; Refenax Jarabe; Tavinex Antigripal; *Austria*: Influbene†; *Switz.*: Bronchotussine†.

Calcium Iodide

Calcii Iodidum; Calciumjodid; Ioduro de calcio; Kalcio jodidas; Kalsiumjodidi; Йодид Кальция.

CaI_2=293.9

CAS — 10102-68-8.

UNII — 8EKI9QEE2H (calcium iodide); 4B9QO6S58D (calcium iodide hexahydrate).

Pharmacopoeias. *Eur.* (see p. vii) includes the tetrahydrate for homoeopathic preparations.

Ph. Eur. 8: (Calcium Iodide Tetrahydrate for Homoeopathic Preparations; Calcii Iodidum Tetrahydricum ad Praeparationes Homoeopathicas). A white or almost white, very hygroscopic, powder. Very soluble to freely soluble in water and in alcohol. Store in airtight containers.

Profile

Calcium iodide has been used orally in expectorant mixtures. The limitations of iodides as expectorants are discussed under Cough, p. 1651.2. The actions of the iodides are discussed under Iodine (p. 2336.3).

Homoeopathy

Calcium iodide has been used in homoeopathic medicines under the following names: Calcium iodatum; Calcium jodatum; Calcarea iodata; Cal. iod.; Calc iod.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Calcidrine; Norisodrine with Calcium Iodide.

Homoeopathic Preparations. *Austria*: Exanginа†; *Canad.*: Barijodeel†; Minerals+; Rexorubia†; *Fr.*: Rexorubia; Scrofularia Compose; *Ger.*: Angina-Gastreu S R1; Lymphaden Lymphdrusentabletten; Mullersche Tabletten; Otimed; *Switz.*: Sinusin; Strumeel N; *Venez.*: Strumeel T.

Carbocisteine *(BAN, rINN)*

AHR-3053; Carbocistein; Carbocisteína; Carbocistéine; Carbocisteinum; Carbocysteine (USAN); Karbocistein; Karbocisteinas; Karbociszein; Karbocystein; Karbocysteina; Karbosisteiini; Karbosistein; LJ-206; Карбоцистеин.

S-Carboxymethyl-L-cysteine.

$C_5H_9NO_4S$=179.2

CAS — 2387-59-9; 638-23-3 (carbocisteine, L-form).

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 740120X53R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn*.

Ph. Eur. 8: (Carbocisteine). A white or almost white, crystalline powder. Practically insoluble in water and in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. A 1% suspension in water has a pH of 2.8 to 3.0. Protect from light.

Incompatibility. UK licensed product information states that mixing carbocisteine with pholcodine linctus causes precipitation of carbocisteine from solution but no information is given on whether this incompatibility is with the pholcodine or some component of the formulation used.

Carbocisteine Lysine *(BANM, rINNM)*

Carbocisteína lísina; Carbocistéine Lysine; Carbocisteinum Lysinum; Carbocysteine Lysine; Карбоцистеина Лизин.

CAS — 49673-81-6.

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 1D1Y95PXXA.

Carbocisteine Sodium *(BANM, rINNM)*

Carbocisteína sódica; Carbocistéine Sodique; Carbocysteine Sodium; Natrii Carbocisteinum; Натрий Карбоцистеин.

CAS — 49673-84-9 (carbocisteine sodium, L-form).

ATC — R05CB03.

ATC Vet — QR05CB03.

UNII — 2UZV9PEJ2N.

Uses and Administration

Carbocisteine is used for its mucolytic activity in respiratory disorders associated with productive cough (p. 1651.2). It is given orally in a dose of 750 mg three times daily, reduced by one-third when a response is obtained. Carbocisteine is also given orally as the sodium or lysine salts.

For doses in children, see below.

Reviews.

1. Macciò A, *et al.* Carbocysteine: clinical experience and new perspectives in the treatment of chronic inflammatory diseases. *Expert Opin Pharmacother* 2009; 10: 693–703.

Administration in children. Children aged from 2 to 5 years may be given oral carbocisteine 62.5 to 125 mg four times daily and those aged 5 to 12 years 250 mg three times daily.

Chronic obstructive pulmonary disease. The value of mucolytic therapy in chronic obstructive pulmonary disease (COPD—p. 1199.1) is controversial. Two studies have reported some improvements in lung function in patients with chronic bronchitis given carbocisteine for up to 6 months,[1,2] but it appeared to have no effect on the number of acute exacerbations.[1] However, later studies[3-5] have reported reductions in the number of acute exacerbations; the number of common colds was also lower in the carbocisteine group in one of the studies.[4] Carbocisteine may also produce some beneficial effects on sputum rheology.[2,6]

1. Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis: a double blind trial with placebo control. *Br J Clin Pract* 1985; 39: 395–8.
2. Aylward M, *et al.* Clinical evaluation of carbocisteine (Mucolex) in the treatment of patients with chronic bronchitis: a double-blind trial with placebo control. *Clin Trials J* 1985; 22: 36–44.
3. Allegra L, *et al.* Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. *Respiration* 1996; 63: 174–80.
4. Yasuda H, *et al.* Carbocisteine reduces frequency of common colds and exacerbations in patients with chronic obstructive pulmonary disease. *J Am Geriatr Soc* 2006; 54: 378–80.
5. Zheng J-P, *et al.* Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet* 2008; 371: 2013–18.
6. Braga PC, *et al.* Identification of subpopulations of bronchitic patients for suitable therapy by a dynamic rheological test. *Int J Clin Pharmacol Res* 1989; IX: 175–82.

Adverse Effects and Precautions

Nausea and gastric discomfort, and gastrointestinal bleeding have occasionally occurred with carbocisteine. Skin rashes have also been reported.

Carbocisteine should be used with caution in patients with a history of peptic ulcer disease because of the risk that mucolytics may disrupt the gastric mucosal barrier.

Effects on endocrine function. Transient hypothyroidism associated with the use of carbocisteine developed in a patient with compromised thyroid function.[1]

1. Wiersinga WM. Antithyroid action of carbocisteine. *BMJ* 1986; 293: 106.

Pharmacokinetics

Carbocisteine is rapidly and well absorbed from the gastrointestinal tract and peak plasma concentrations occur about 2 hours after an oral dose. It appears to penetrate into lung tissue and respiratory mucus. Carbocisteine is excreted in the urine as unchanged drug and metabolites. Acetylation, decarboxylation, and sulfoxidation have been identified as the major metabolic pathways. Sulfoxidation may be governed by genetic polymorphism.

References.

1. Karim EFIA, *et al.* An investigation of the metabolism of S-carboxymethyl-L-cysteine in man using a novel HPLC-ECD method. *Eur J Drug Metab Pharmacokinet* 1988; 13: 253–6.
2. Brockmoller J, *et al.* Evaluation of proposed sulphoxidation pathways of carbocysteine in man by HPLC quantification. *Eur J Clin Pharmacol* 1991; 40: 387–92.
3. Steventon GB. Diurnal variation in the metabolism of S-carboxymethyl-L-cysteine in humans. *Drug Metab Dispos* 1999; 27: 1092–7.
4. Jovanovic D, *et al.* A comparative bioavailability study of a generic capsule formulation containing carbocysteine. *Pharmazie* 2006; 61: 446–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Mucolitic; Pectox; Salvitos; *Belg.*: Balsoclase Mucolyticum; Broncho-pectoralis Carbocisteine; Muco Rhinathiol; Romilar Mucolyticum†; Siroxyl; Soludril Expectorans; *Braz.*: Carbocin; Carbofan; Carbotoss; Certuss†; Fluilitic; Fluitoss; Mucocist†; Mucocistein; Mucofan; Mucoflux; Mucolab; Mucolisil; Mucolitic; Mucolixt†; Mucotoss; Santoss; *Chile*: Broncotusilan; Carbotos; Coldin; *China*: Bai Yue (百越); Baling (翁灵); Kang Pu Li (康普利); Cz.: Fenorin; Pectodrill; Sinecosin; *Fin.*: Reodyn; *Fr.*: Bronchathiol; Bronchokod; Broncoclar; Bronkirex†; Clarix Expectorant; Drill Expectorant; Ergix Expectorant; Exotoux; Fluditec; Fluvic†; Humex Expectorant; Medibronc; Muciclar†; Pharmakod expectorant†; Rhinathiol; Tussilene†; *Ger.*: Transbronchin; *Gr.*: Allstam; Bronchiole; Ceflavit; Chilvax; Convenil; Divallo; Drizak; Duxil; Dynax; Ectofus; Estival; Grossenel; Methovix; Mucopront; Mucorem; Mucothiol; Neo-Adinal; Nystetrin; Pneumol; Pulmoclase; Santamex-Expectorant; Siroxyl; Trusil; *Hong Kong*: Fluifort; Mucosin; Mucospect; Purasol†; Rhinathiol; Solmux; *Hung.*: Drill Expectorant; Drill; Fenorin; Mucopront; NeoCitran Expectorant†; Rhinathiol; Solucis†; *India*: Mucodyne; *Indon.*: Broncholit; Mucocil†; Solmux†; *Irl.*: Benylin Mucus Relief; Exputex; Mucodyne; Mucogen†; Mucolex†; PectoDrill; Pulmoclase†; Unicough Chesty; Viscolex; *Israel*: Mical; Muco-Treat; Mucolit; Mucomed; Mucosol†; *Ital.*: Broncomucil†; Fluicare; Fluifort; Lisomucil; Mucocis; Mucolase; Mucostar; Mucotreis; Polimucil; Recofluid; Sinecod Tosse Fluidificante; Solucis; *Jpn*: Mucodyne; *Malaysia*: Fluifort; Kastipron; Pabron Cough; Rhinathiol; SCMC; *Mex.*: Arbistin; Expelin; Mucolin Pediatrico; *Neth.*: Dampo Solvopect†; Mucodyne; Rami Slijmoplossende†; Rhinathiol; *Philipp.*: Abluent†; Aflem; Ameustyn; Bromycil; Broncocent; Broxytone; Bysbalon; Carboflem; Carbomed; Carbosol†; Ceascol; CRB; Cysdexpel; Emuxel†; Esboxyl; Fayerex; Flemsol; Fluralex; Genecar; Lofenin; Loviscol; Mediphlegm; Nivicof; Pediaplex; Pertussin; Phlegmol; Pulmin-CMC; S-Muxine; Solmux; Solplem†; Trimulex; Viscodec; Westcarbox; Zylotin; Zymelytic; *Pol.*: Mukolina; PectoDrill; *Port.*: Drill Mucolitico; Finatux; Griflux; Mucolex†; Mucorespiral; Mucorhinathiol Infantil†; Mucorhinathiol Mucoral; Pulmiben; *Rus.*: Bronchobos (Бронхобос); Fluditec (Флюдитек); Fluifort (Флуифорт); Libexin Muco (Либексин Муко); Mucodin (Мукодин); Mucosol (Мукосол); *S.Afr.*: Acuphlem†; Betaphlem; Bronchette; Co-Flem; Dis-chem; Flemex; Flemgo; Flemlite; Flutex; Lessmusec; Medphlem†; Mucoflem†; Mucoless; Mucolinct†; Mucopan; Mucosol; Mucospect; *Singapore*: Mucodin; Mucon; Rhinathiol; Robitussin CM; SCMC; Solmux; SP-Mucoplex; *Spain*: Actithiol; Anatac; Cinfamucol; Cisbedal; Fluidin Mucolitico; Frimuce; Iniston Mucolitico; Mucovital; Pectodrill; Pectox; Viscoteina; *Switz.*: MAKU Mucolytique†; Mephathiol-Mucogeran†; Mucoseptal; Pectorex Mucolytique; Pectox; Rhinathiol; Rhinatussol; Rotpunkt Apotheke Mucolytique Sirop†; Tussantiol; *Thal.*: Amicof; Bocytin; Carbocter; Carbocys; Carbomed; Carbopect; Carsemex; Cisteine; Copharmex; Exflem; Expetan; Flemex; Fluifort; I-Cof; Mucolex; Mucomex; Muflex; Murhinol; Rhinamex; Rhinathiol; Rhinatol; Rhinex; Siflex; Solmux†; Throatsil-CBS; *Turk.*: Mucobron; Mucosis; Mukoliz; Mukotik; *UK*: Mucodyne; *Ukr.*: Fluditec (Флюдитек); Langes (Лангес); *Venez.*: Broxolflem; Gulaper; Loganil; Loviscol; Mucofar; Mucopront.

Multi-ingredient Preparations. *Arg.*: Mucolitic Antitusivo; *China*: Bang Ao Shu (邦奥舒); Kai Yin (凯茵); *Fr.*: Rhinathiol Promethazine; *Gr.*: Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Tussifren; Vanesin; *Hong Kong*: Mucoprom; Rhinathiol Promethazine; *India*: Caceff; Carbasma; Carbicef; Carbomox; Carlymox; Carmox; Cecarb; Cidoresp; Cismox; Cystamox; Moxycarb; Mucobron; Muconal; *Ital.*: Keraflex; Libexin Mucolitico; *Malaysia*: CP Cough Syrup; Mucoease Plus; Mucoprom; Rhinathiol Promethazine; *Mex.*: Mucolin; *Philipp.*: Solmux-Broncho (Reformulated); *Port.*: Bronquial; Niflux; *Singapore*: Rhinathiol Promethazine; *Spain*: Actithiol Antihist; Bronquicisteina†; Eduprim Mucolitico†; *Switz.*: Rhinathiol Promethazine†; Triofan Rhume; *Ukr.*: Millstan Cough (Миістан Кашлю); Pectolvan C (Пектолван Ц).

Clobutinol Hydrochloride *(rINNM)*

Clobutinol, Chlorhydrate de; Clobutinol, hidrocloruro de; Clobutinoli Hydrochloridum; Hidrocloruro de clobutinol; KAT-256; Клобутинола Гидрохлорид.

2-(4-Chlorobenzyl)-3-(dimethylaminomethyl)butan-2-ol hydrochloride.

$C_{14}H_{22}ClNO.HCl$=292.2

CAS — 14860-49-2 (clobutinol); 1215-83-4 (clobutinol hydrochloride).

ATC — R05DB03.

ATC Vet — QR05DB03.
UNII — N2U6799DZQ.

Profile

Clobutinol hydrochloride is a centrally acting cough suppressant for non-productive cough (p. 1651.2) that has been given orally in doses of 40 to 80 mg three times daily; it has also been given by subcutaneous, intramuscular, or intravenous injection. However, the EMEA has recommended for its withdrawal due to the risk of QT interval prolongation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Proking; ***Chile***: Broncodual; Calfetos; Clobotil; Cloval; Pulbronc Simple; ***Gr.***: Silomat.

Multi-ingredient Preparations. ***Arg.***: Bronquisedan Mucolitico; ***Braz.***: Hytos Plus; ***Chile***: Broncodual Compuesto; Cloval Compuesto; Pulbronc; Solvanol; Tusabron†; Vapoflu; ***Gr.***: Silomat Compositum; ***Indon.***: Silomat Compositum†; ***UAE***: Orclnol†.

Clofedanol Hydrochloride *(BANM, rINNM)*

Chlophedianol Hydrochloride (USAN); Clofédanol, Chlorhydrate de; Clofedanol, hidrocloruro de; Clofedanoli Hydrochloridum; Hidrocloruro de clofedanol; SL-501; Клофеданола Гидрохлорид.

2-Chloro-α-(2-dimethylaminoethyl)benzyl alcohol hydrochloride.

$C_{17}H_{20}ClNO,HCl$=326.3

CAS — 791-35-5 (clofedanol); 511-13-7 (clofedanol hydrochloride).
ATC — R05DB10.
ATC Vet — QR05DB10.
UNII — 69QQ58998Y.

Pharmacopoeias. In *Jpn*.

Profile

Clofedanol hydrochloride is a centrally acting cough suppressant for non-productive cough (p. 1651.2) that has been given in oral doses of 25 mg three or four times daily. For doses in children, see below.

Administration in children. The following oral doses of clofedanol hydrochloride have been recommended for children:

- 2 to 6 years: 12.5 mg 3 or 4 times daily
- 6 to 12 years: 12.5 to 25 mg 3 or 4 times daily

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Canad.***: Ulone.

Multi-ingredient Preparations. ***Arg.***: Causalon Bronquial; Cofron; Notozen†; Pectoral Hebert; Selectus FN; Toxam; Toxambay; ***Chile***: Bauxol; Brontal; Diadicon; Esantuss; Kolibel; Mucobrol; Plus-Tos; ***USA***: Biclora-D; Biclora; Certuss-D; Chlo Tuss EX; Clofera; Dicel CD; Donatussin; DryMax AF; Prohist CF; Vanacof APE; Vanacof DX; Vanacof GPE; Vanacof-8.

Clonazoline Hydrochloride *(rINNM)* ⊗

Clonazoline; Chlorhydrate de; Clonazolini Hydrochloridum; Hidrocloruro de clonazolina; Клоназолина Гидрохлорид.

2-[(4-Chloro-1-naphthyl)methyl]-2-imidazoline hydrochloride.

$C_{14}H_{13}ClN_2,HCl$=281.2

CAS — 17692-28-3 (clonazoline); 23593-08-0 (clonazoline hydrochloride).

Profile

Clonazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3) used for its vasoconstrictor activity in the local treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Ital.***: Localyn.

Cloperastine *(rINN)*

Cloperastina; Cloperastine; Cloperastinum; HT-11; Клоперастин.

1-[2-[(*p*-Chloro-α-phenylbenzyl)oxy]ethyl]piperidine.

$C_{20}H_{24}ClNO$=329.9

CAS — 3703-76-2 (cloperastine); 132301-89-4 (levocloperastine).
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — 69M5L7BXEK.

Cloperastine Fendizoate *(rINNM)*

Cloperastina, fendizoato de; Clopérastine, Fendizoate de; Cloperastine Hydroxyphenylbenzoyl Benzoic Acid; Cloperastine Phendizoate; Cloperastini Fendizoas; Fendizoato de cloperastina; Клоперастина Фендизоат.

$C_{20}H_{24}ClNO,C_{20}H_{14}O_4$=648.2

CAS — 85187-37-7 (cloperastine fendizoate); 220329-19-1 (levocloperastine fendizoate).
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — 2M105305SU.

Cloperastine Hydrochloride *(rINNM)*

Cloperastina, hidrocloruro de; Clopérastine, Chlorhydrate de; Cloperastini Hydrochloridum; Hidrocloruro de cloperastina; Клоперастина Гидрохлорид.

$C_{20}H_{24}ClNO,HCl$=366.3

CAS — 14984-68-0.
ATC — R05DB21.
ATC Vet — QR05DB21.
UNII — PI4N7C63ND.

Pharmacopoeias. In *Jpn*.

Profile

Cloperastine is primarily a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It also has some antihistaminic action. The hydrochloride has been given orally as tablets in usual doses of 10 to 20 mg three times daily. Cloperastine fendizoate is used in oral liquid preparations in equivalent doses. Cloperastine fendizoate 17.7 mg is equivalent to about 10 mg of cloperastine hydrochloride. Levocloperastine fendizoate has been used similarly.

References.

1. Aliprandi P, *et al.* Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. *Drugs Exp Clin Res* 2004; 30: 133–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Belg.***: Lysotossil; Sekin; ***Braz.***: Seki; Tilugen; ***Hong Kong***: Uncough; ***Ital.***: Cloel; Clofend; Mitituss; Nitossil; Novotossil; Politosse; Privituss; Quik; Seki; ***Jpn***: Hustazol; ***Malaysia***: Copastin; ***Mex.***: Privituss; Sekisan; ***Port.***: Tecnofox; ***Spain***: Flutox; Sekisan.

Multi-ingredient Preparations. ***Thai.***: Hustazol-C.

Cocillana

Grape Bark; Guapi Bark; Huapi Bark; Коккилана.

CAS — 1398-77-2.
ATC Herb — HR05WA5017 (Guarea guidonia: bark).

Profile

Cocillana is the dried bark of *Guarea guidonia* (*G. rusbyi, Sycocarpus rusbyi, G. trichilioides*) (Meliaceae), a South American tree. It is used as an expectorant similarly to ipecacuanha (p. 1667.2). It has been used in large doses as an emetic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Fin.***: Codetabs.

Multi-ingredient Preparations. ***Canad.***: Sirop Cocillana Codeine; ***Fin.***: Codesan Comp; ***Hong Kong***: Co-Epherine†; Coci-Fedra-C†; Coci-Fedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Compound Cocillana†; Coolding†; Dextrocilla; Eurocilana; ***Ital.***: Broncosedina; Broncosedina; ***S. Afr.***: Adco-Cocillana Co; Corbar; ***Swed.***: Cocillana-Etyfin; ***Venez.***: Cerylana.

Coltsfoot

Coughwort; Farfara; Huflattich; Tusilago; Tussilage; Камчужная Трава.

ATC Herb — HR05WA5060 (Tussilago farfara: flower); HR05WA5061 (Tussilago farfara: leaf); HR05WA5062 (Tussilago farfara: whole plant).
UNII — 6177A89GA2 (Tussilago farfara); UEE27X2Q2M (Tussilago farfara flower); 6WBB6U5V2Q (Tussilago farfara flower bud); 0JXZ63016V (Tussilago farfara flowering); G2GH7V846Z (Tussilago farfara leaf); E02X1126ZN (Tussilago farfara root).

Pharmacopoeias. *Chin.* and *Fr.* include Coltsfoot Flower.

Profile

The leaves and flowers of coltsfoot (*Tussilago farfara*) have been used for their demulcent and supposed expectorant properties in the treatment of cough and other mild respiratory disorders. However, there has been some concern about potential hepatotoxicity and carcinogenicity due to the content of pyrrolizidine alkaloids.

A review[1] of the actions and uses of coltsfoot pointed out that given the potential risks of its use long-term or in pregnancy, and the availability of other demulcent herbs, the use of coltsfoot preparations to treat throat irritations can no longer be considered appropriate.

1. Berry M. Coltsfoot. *Pharm J* 1996; 256: 234–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Pol.***: Parfaron.

Multi-ingredient Preparations. ***Arg.***: Arceligasol; Negacne; ***Canad.***: Herbal Cough Syrup†; ***Cz.***: Species Pectorales Planta; ***Fr.***: Mediflor Pectorale d'Alsace no 8†; ***Ital.***: Lozione Same Urto; ***Pol.***: Mucosit; Pyrosal; ***Rus.***: Fitantus (Фитантус); Pectorales Species No 1 (Грудной Сбор 1); Pectorales Species No 2 (Грудной Сбор 2); ***UK***: Antibron; Chesty Cough Relief.

Homoeopathic Preparations. ***Fr.***: Hamamelis Compose; Poconeol no 24; Poconeol no 55; ***Ger.***: Jsostoma S; Roth's RKT Tropfen.

Creosote

Creasote; Creosota; Creosotal (creosote carbonate); Wood Creosote; Древесный Креозот.

CAS — 8021-39-4 (creosote); 8001-59-0 (creosote carbonate).
ATC — R05CA08.
ATC Vet — QR05CA08.
UNII — 3JYG22FD73.

Pharmacopoeias. In *Jpn*.

Profile

Creosote is a liquid consisting of a mixture of guaiacol, cresol, and other phenols obtained from wood tar. It possesses disinfectant properties and has been used as an expectorant. It has also been used as the carbonate and as lactocreosote.

Adverse effects are similar to those of Phenol, p. 1764.2.

Commercial creosote used for timber preservation is obtained from coal tar.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: Compound Inhalation of Menthol†; ***Austria***: Famel cum Codein†; Famel cum Ephedrin†; ***Braz.***: Rhum Creosotado†; ***Fr.***: Pulperyl; Sedapulpe†; Yranol Eugenole; ***Hong Kong***: Nisshin Seirogan†; ***India***: Mynberrys Compound; Pulm-Cod (C & G); ***Ital.***: Creosoto Composto; ***UK***: Famel Original.

Homoeopathic Preparations. ***Austral.***: Teething Relief; ***Austria***: Bronchalis-Heel; ***Canad.***: Bronkeel†; Hylands Vaginitis†; ***Cz.***: Bronchalis-Heel; Lamioflur†; ***Fr.***: Boripharm No 11†; Conium Complexe No 36†; Diabene; Hedera Complexe No 120; Homeodose 8†; Kreosotum Complexe No 62; ***Ger.***: Aletris Oligoplex†; Arte-cyl Ho-Len-Complex; Hewelymphon N†; Mucosa compositum; Prostata-Entoxin N; Sinupas; Ulco-cyl L Ho-Len-Complex; ***Hung.***: Bronchalis-Heel; ***Neth.***: Bronchalis; Mucosa comp H; Ricura; ***Rus.***: Plantago-Plus (Плантаго-Плюс); ***Switz.***: Bronchalis-Heel; Regenaplex Nr. 59b.

Dembrexine *(BAN, rINN)*

Dembrekslini; Dembrexin; Dembrexina; Dembrexinum; Dembroxol; Дембрексин.

trans-4-[(3,5-Dibromosalicyl)amino]cyclohexanol.

$C_{13}H_{17}Br_2NO_3$=395.1

CAS — 83200-09-3 (dembrexine); 52702-51-9 (dembrexine hydrochloride).
UNII — 4F61F502TS.

Pharmacopoeias. In *Eur.* (see p. vii) for veterinary use only.

Ph. Eur. 8: (Dembrexine Hydrochloride Monohydrate for Veterinary Use; Dembrexine Hydrochloride Monohydrate

BP(Vet) 2014). A white or almost white, crystalline powder. Slightly soluble in water and in anhydrous ethanol; freely soluble in methyl alcohol.

Profile

Dembrexine is a mucolytic used as the hydrochloride in veterinary medicine.

Denufosol Tetrasodium *(USAN, rINNM)*

Denufosol tetrasódico; Denufosol tetrasodique; Denufosolum tetranatricum; INS-37217; Денуфозол Тетранатрий.

2′-Deoxycytidine(5′)tetraphospho(5′)uridine tetrasodium.

$C_{18}H_{23}N_5Na_4O_{21}P_4$=861.3

CAS — 211448-85-0 (denufosol); 318250-11-2 (denufosol tetrasodium).

UNII — 82M942WZ4A.

Profile

Denufosol tetrasodium is a selective $P2Y_2$-receptor agonist that stimulates chloride and water secretion from respiratory tract epithelial cells, and increases mucosal hydration and mucociliary clearance. An inhaled preparation is under investigation for the treatment of cystic fibrosis.

References.

1. Cole P, *et al.* Denufosol tetrasodium. *Drugs Of The Future* 2008; 33: 668–72.

Dextromethorphan *(BAN, pINN)*

Dekstrometorfaani; Dextrométhorphane; Dextromethorphanum; Dextrometorfan; Dextrometorfano; Декстрометорфан.

(+)-3-Methoxy-9a-methylmorphinan; (9*S*,13*S*,14*S*)-6,18-Dideoxy-7,8-dihydro-3-*O*-methylmorphine.

$C_{18}H_{25}NO$=271.4.

CAS — 125-71-3.

ATC — R05DA09.

ATC Vet — QR05DA09.

UNII — 7355X3ROTS.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of dextromethorphan:

Bromage; Brome; Candy; CCC; C-C-C; Dex; Dextro; DM; Dmx; Drex; DXM; Red Devils; Robo; Rojo; Rowbowing; Skittles; Skittling; Snurf; Triple C; Triple C's; Tussin; Velvet; Vitamin D.

Pharmacopoeias. In *US.*

USP 36: (Dextromethorphan). A practically white to slightly yellow, odourless, crystalline powder. Practically insoluble in water; freely soluble in chloroform. Store in airtight containers.

Dextromethorphan Hydrobromide

(BANM, pINNM)

Dekstrometorfaanihydrobromidi; Dekstrometorfan Hidrobromür; Dekstrometorfano hidrobromidas; Dekstrometorfanu bromowodorek; Dextromethorfan-hydrobromid monohydrát; Dextrométhorphane, Bromhydrate de; Dextromethorphanhydrobromid; Dextromethorphani hydrobromidum; Dextromethorphani Hydrobromidum Monohydricum; Dextrometorfán-hidrobromid; Dextrometorfanhydrobromid; Dextrometorfano, hidrobromuro de; Hidrobromuro de dextrometorfano; Декстрометорфана гидробромид.

Dextromethorphan hydrobromide monohydrate.

$C_{18}H_{25}NO,HBr,H_2O$=370.3

CAS — 125-69-9 (anhydrous dextromethorphan hydrobromide); 6700-34-1 (dextromethorphan hydrobromide monohydrate).

ATC — R05DA09.

ATC Vet — QR05DA09.

UNII — 9D2RTI9KYH (dextromethorphan hydrobromide); Z0CG3115FG (anhydrous dextromethorphan hydrobromide).

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Dextromethorphan Hydrobromide). An almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol. Protect from light.

USP 36: (Dextromethorphan Hydrobromide). Practically white crystals or crystalline powder having a faint odour. Soluble 1 in 65 of water; freely soluble in alcohol and in chloroform; insoluble in ether. pH of a 1% solution in water is between 5.2 and 6.5. Store in airtight containers.

Uses and Administration

Dextromethorphan hydrobromide is a cough suppressant used for the relief of non-productive cough (below); it has a central action on the cough centre in the medulla. It is also an antagonist of *N*-methyl-D-aspartate (NMDA) receptors and a σ-receptor agonist. Although structurally related to morphine, dextromethorphan has no classical analgesic properties (but see Pain, below) and little sedative activity.

As a cough suppressant dextromethorphan hydrobromide is reported to act within half an hour of an oral dose and to exert an effect for up to 6 hours. It is given orally in doses of 10 to 20 mg every 4 hours, or 30 mg every 6 to 8 hours, to a usual maximum of 120 mg in 24 hours.

Dextromethorphan polistirex (a dextromethorphan and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release oral preparations. The dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, is the equivalent of 60 mg every 12 hours.

Dextrorphan (p. 2492.3), the *O*-demethylated metabolite of dextromethorphan, also has cough suppressant properties.

For doses in children, see below.

Dextromethorphan is also used in the treatment of pseudobulbar affect associated with amyotrophic lateral sclerosis and multiple sclerosis (see Neurological Disorders, below). It is given with low-dose quinidine which increases the bioavailability of dextromethorphan by inhibiting its metabolism. It is given as a fixed oral dose combination of dextromethorphan hydrobromide 20 mg and quinidine sulfate 10 mg. The dextromethorphan is given at a starting dose of 20 mg daily for 7 days followed by a maintenance dose of 20 mg twice daily.

Administration in children. Although dextromethorphan hydrobromide is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in young children, for details see p. 1651.2 and also Cough, below.

In the USA, the following oral doses have been given according to age:

- 4 to 6 years: 2.5 to 5 mg every 4 hours, or 7.5 mg every 6 to 8 hours, to a maximum of 30 mg in 24 hours
- 6 to 12 years: 5 to 10 mg every 4 hours or 15 mg every 6 to 8 hours, to a maximum of 60 mg in 24 hours

Dextromethorphan polistirex is used in modified-release oral preparations. The following dosage of dextromethorphan polistirex, expressed as dextromethorphan hydrobromide, has been given to children:

- 2 to 6 years: 15 mg every 12 hours
- 6 to 12 years: 30 mg every 12 hours

Cough. Equal doses of dextromethorphan hydrobromide and codeine phosphate were of similar efficacy in reducing the frequency of chronic cough (p. 1651.2) in a double-blind crossover study in adults, but dextromethorphan had a greater effect than codeine on cough intensity.[1] However, these drugs were little more effective than placebo in suppressing night-time cough in children.[2-4] The American Academy of Pediatrics has commented[5] that there is no good evidence for the antitussive efficacy of dextromethorphan in children, that dosage guidelines are derived from (possibly inappropriate) extrapolation from effects in adults, and that adverse effects have been reported. Furthermore, in 2008, the FDA and the MHRA advised that over-the-counter cough and cold preparations containing cough suppressants (including dextromethorphan) should be used with caution in children and generally avoided in those under 2 years of age. In 2009, after further review, the MHRA advised that such preparations should also be avoided in children aged under 6 years. For further details, see p. 1651.2.

There is also some evidence that genetic polymorphism in the cytochrome P450 isoenzyme CYP2D6, and hence variations in metabolism, may have a significant influence on the antitussive efficacy of dextromethorphan.[6]

1. Matthys H, *et al.* Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983; 11: 92–100.
2. Gadomski A, Horton L. The need for rational therapeutics in the use of cough and cold medicine in infants. *Pediatrics* 1992; 89: 774–6.
3. Taylor JA, *et al.* Efficacy of cough suppressants in children. *J Pediatr* 1993; 122: 799–802.
4. Paul IM, *et al.* Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004; 114: e85–e90.
5. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics* 1997; 99: 918–20. [Re-affirmed October 2006] Also available at: http://pediatrics.aappublications.org/cgi/reprint/99/6/918.pdf (accessed 11/05/07)
6. Wright CE, *et al.* CYP2D6 polymorphism and the anti-tussive effect of dextromethorphan in man. *Thorax* 1997; 52 (suppl 6): A73.

Neurological disorders. Dextromethorphan appears to have anticonvulsant activity and may have neuroprotective effects in cerebral ischaemia.[1] These effects may be related to its activity as an antagonist of *N*-methyl-D-aspartate (NMDA) receptors or to interaction with σ-receptors. It has been studied in Parkinson's disease for treatment[2] or for management of levodopa-induced dyskinesias,[3] and for its potential protective action in stroke and acute brain injury.

Dextromethorphan has also been studied for the management of amyotrophic lateral sclerosis (see Motor Neurone Disease, p. 2605.2) but was not found to be of benefit.[4-6] However, studies indicated that the combination of dextromethorphan and quinidine was effective in treating pseudobulbar affect (emotional lability) associated with amyotrophic lateral sclerosis[7,8] and multiple sclerosis[8,9] The addition of quinidine inhibits the metabolism of the dextromethorphan increasing its bioavailability.[10]

The NMDA-antagonist properties of dextromethorphan have also been investigated for the treatment[11,12] of nonketotic hyperglycinaemia (p. 2623.2).

1. Tortella FC, *et al.* Dextromethorphan and neuromodulation: old drug coughs up new activities. *Trends Pharmacol Sci* 1989; 10: 501–7.
2. Bonuccelli U, *et al.* Dextromethorphan and parkinsonism. *Lancet* 1992; 340: 53.
3. Verhagen Metman L, *et al.* Dextromethorphan improves levodopa-induced dyskinesias in Parkinson's disease. *Neurology* 1998; 51: 203–6.
4. Askmark H, *et al.* A pilot trial of dextromethorphan in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1993; 56: 197–200.
5. Blin O, *et al.* A controlled one-year trial of dextromethorphan in amyotrophic lateral sclerosis. *Clin Neuropharmacol* 1996; 19: 189–92.
6. Gredal O, *et al.* A clinical trial of dextromethorphan in amyotrophic lateral sclerosis. *Acta Neurol Scand* 1997; 96: 8–13.
7. Brooks BR, *et al.* Treatment of pseudobulbar affect in ALS with dextromethorphan/quinidine: a randomized trial. *Neurology* 2004; 63: 1364–70.
8. Pioro EP, *et al.* Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol* 2010; 68: 693–702.
9. Panitch HS, *et al.* Randomized, controlled trial of dextromethorphan/quinidine for pseudobulbar affect in multiple sclerosis. *Ann Neurol* 2006; 59: 780–7.
10. Rosen H. Dextromethorphan/quinidine sulfate Zenvia for pseudobulbar affect. *Drugs Today* 2008; 44: 661–8.
11. Alemzadeh R, *et al.* Efficacy of low-dose dextromethorphan in the treatment of nonketotic hyperglycinemia. *Pediatrics* 1996; 97: 924–6.
12. Hamosh A, *et al.* Long-term use of high-dose benzoate and dextromethorphan for the treatment of nonketotic hyperglycinemia. *J Pediatr* 1998; 132: 709–13.

Pain. Dextromethorphan has a potential role in the blockade of pain. It has been investigated[1-3] in the management of neuropathic pain with promising results in diabetic neuropathy (p. 8.2), although pain was not reduced in postherpetic neuralgia (p. 10.3). High doses of dextromethorphan may be needed for an effect, or combination with quinidine, which inhibits dextromethorphan metabolism.[4] However, the use of dextromethorphan in diabetic neuropathy remains investigational.[5]

A systematic review[6] of 28 studies of dextromethorphan as an adjunct for postoperative pain found that despite a tendency for patients to report less pain than with placebo, and to use less opioid analgesia postoperatively, the differences tended to be inconsistent and of questionable clinical significance. There was some suggestion that parenteral dextromethorphan was more effective than oral.

1. Nelson KA, *et al.* High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997; 48: 1212–18.
2. Sang CN, *et al.* Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology* 2002; 96: 1053–61.
3. Carlsson KC, *et al.* Analgesic effect of dextromethorphan in neuropathic pain. *Acta Anaesthesiol Scand* 2004; 48: 328–36.
4. Thissed RA, *et al.* Dextromethorphan and quinidine in adult patients with uncontrolled painful diabetic peripheral neuropathy: a 29-day, multicenter, open-label, dose-escalation study. *Clin Ther* 2006; 28: 1607–18.
5. Criner TM, Perdun CS. Dextromethorphan and diabetic neuropathy. *Ann Pharmacother* 1999; 33: 1221–3.
6. Duedahl TH, *et al.* A qualitative systematic review of peri-operative dextromethorphan in post-operative pain. *Acta Anaesthesiol Scand* 2006; 50: 1–13.

Adverse Effects and Treatment

Adverse effects with dextromethorphan appear to be rare and may include dizziness and gastrointestinal disturbances. Excitation, confusion, and respiratory depression may occur after overdosage. Dextromethorphan has been subject to abuse, but there is little evidence of dependence of the morphine type.

General references.

1. Bem JL, Peck R. Dextromethorphan: an overview of safety issues. *Drug Safety* 1992; 7: 190–9.

Hypersensitivity. A fixed-drug reaction developed in a patient after ingestion of dextromethorphan 30 mg.[1] Oral provocation with dextromethorphan produced a positive reaction but the results of topical application tests were negative. Urticaria, angioedema, and shortness of breath were reported in another patient;[2] symptoms recurred on oral challenge, but no skin test was performed. Similar symptoms were reported in a third patient;[3] skin testing

provoked a positive reaction. On oral rechallenge, the patient developed urticaria initially, followed by generalised erythema and pruritus and decreased blood pressure after a second dose.

1. Stubb S, Rettamo S. Fixed-drug eruption due to dextromethorphan. *Arch Dermatol* 1990; 126: 970–1.
2. Knowles SR, Weber E. Dextromethorphan anaphylaxis. *J Allergy Clin Immunol* 1998; 102: 316–17.
3. Robledo T, *et al.* Adverse reaction to dextromethorphan. *Allergy* 2004; 59: 890.

Overdosage. There have been reports[1-7] of overdosage or accidental poisoning (usually in children) due to dextromethorphan, including rare fatalities. Naloxone may be effective in reversing toxicity. Extrapyramidal reactions were seen in a child who ingested dextromethorphan.[6] Overdosage has also been associated with abuse (see below).

1. Shaul WL, *et al.* Dextromethorphan toxicity: reversal by naloxone. *Pediatrics* 1977; 59: 117–19.
2. Katona B, Wason S. Dextromethorphan danger. *N Engl J Med* 1986; 314: 993.
3. Rammer L, *et al.* Fatal intoxication by dextromethorphan: a report on two cases. *Forensic Sci Int* 1988; 37: 233–6.
4. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; 9: 237–8.
5. Pender ES, Parks BR. Toxicity with dextromethorphan-containing preparations: a literature review and report of two additional cases. *Pediatr Emerg Care* 1991; 7: 163–5.
6. Warden CR, *et al.* Dystonic reaction associated with dextromethorphan ingestion in a toddler. *Pediatr Emerg Care* 1997; 13: 214–15.
7. Roberge RJ, *et al.* Dextromethorphan- and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; 17: 285–8.

Precautions

Dextromethorphan should not be given to patients at risk of developing respiratory failure. Caution is needed in patients with a history of asthma and it should not be given during an acute attack. Care is also advisable in patients with bronchitis, emphysema, or in other conditions where chronic or persistent cough occurs.

Abuse. Dextromethorphan has been abused,[1-11] alone or with other drugs in over-the-counter preparations or as a powder sold under the name DXM. There have been a few reports of dependence,[1,2,10] but evidence of classical opioid dependence is generally considered to be lacking.

1. Fleming PM. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; 293: 597.
2. Orrell MW, Campbell PG. Dependence on dextromethorphan hydrobromide. *BMJ* 1986; 293: 1242–3.
3. Walker J, Yatham LN. Benylin (dextromethorphan) abuse and mania. *BMJ* 1993; 306: 896.
4. Wolfe TR, Caravati EM. Massive dextromethorphan ingestion and abuse. *Am J Emerg Med* 1995; 13: 174–6.
5. Nordt SP. DXM: a new drug of abuse? *Ann Emerg Med* 1998; 31: 794–5.
6. Cranston JW, Yoast R. Abuse of dextromethorphan. *Arch Fam Med* 1999; 8: 99–100.
7. Price LH, Lebel J. Dextromethorphan-induced psychosis. *Am J Psychiatry* 2000; 157: 304.
8. Noonan WC, *et al.* Dextromethorphan abuse among youth. *Arch Fam Med* 2000; 9: 791–2.
9. Banerji S, Anderson IB. Abuse of Coricidin HBP cough and cold tablets: episodes recorded by a poison center. *Am J Health-Syst Pharm* 2001; 58: 1811–14.
10. Desai S, *et al.* Chronic addiction to dextromethorphan cough syrup: a case report. *J Am Board Fam Med* 2006; 19: 320–3.
11. Bryner JK, *et al.* Dextromethorphan abuse in adolescence: an increasing trend: 1999–2004. *Arch Pediatr Adolesc Med* 2006; 160: 1217–22.

Children. For doubts about the use of dextromethorphan as an antitussive in children see Cough, under Uses and Administration, p. 1660.2.

Interactions

Severe and sometimes fatal reactions have been reported after use of dextromethorphan in patients receiving MAOIs. Dextromethorphan is primarily metabolised by the cytochrome P450 isoenzyme CYP2D6; the possibility of interactions with inhibitors of this enzyme, including amiodarone, haloperidol, propafenone, quinidine, SSRIs, and thioridazine, should be borne in mind.

Antiarrhythmics. *Quinidine* can increase serum concentrations of dextromethorphan markedly, and some patients have had symptoms of dextromethorphan toxicity when the two drugs have been used together.[1,2] Based on this interaction, the combination has been studied for its therapeutic effect in amyotrophic lateral sclerosis and pseudobulbar affect (see Neurological Disorders, p. 1660.3). *Amiodarone* also appears to be able to increase serum concentrations of dextromethorphan.[3]

1. Zhang Y, *et al.* Dextromethorphan: enhancing its systemic availability by way of low-dose quinidine-mediated inhibition of cytochrome P4502D6. *Clin Pharmacol Ther* 1992; 51: 647–55.
2. Pope LE, *et al.* Pharmacokinetics of dextromethorphan after single or multiple dosing in combination with quinidine in extensive and poor metabolizers. *J Clin Pharmacol* 2004; 44: 1132–42.
3. Funck-Brentano C, *et al.* Influence of amiodarone on genetically determined drug metabolism in humans. *Clin Pharmacol Ther* 1991; 50: 259–66.

Antibacterials. Serotonin syndrome-like symptoms have occurred when dextromethorphan has been taken with *linezolid*.

Antidepressants. A patient receiving *fluoxetine* had visual hallucinations after she began taking dextromethorphan.[1] The hallucinations were similar to those she had had 12 years earlier with lysergide. She had previously taken dextromethorphan alone without any adverse reactions. A serotonin syndrome (p. 443.2) has been reported in a patient who took a cold-remedy containing dextromethorphan while receiving *paroxetine*.[2]

1. Achamallah NS. Visual hallucinations after combining fluoxetine and dextromethorphan. *Am J Psychiatry* 1992; 149: 1406.
2. Skop BP, *et al.* The serotonin syndrome associated with paroxetine, an over-the-counter cold remedy, and vascular disease. *Am J Emerg Med* 1994; 12: 642–4.

Pharmacokinetics

Dextromethorphan is rapidly absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged dextromethorphan and demethylated metabolites including dextrorphan (p. 2492.3), which has some cough suppressant activity.

Genetic polymorphism. The *O*-demethylation of dextromethorphan and the hydroxylation of debrisoquine are under common polymorphic control, involving the cytochrome P450 isoenzyme CYP2D6, and dextromethorphan has been used as an alternative to debrisoquine (p. 1350.1) for the phenotyping of oxidative metabolism.[1,2] Non-invasive determinations can be made using samples of urine or saliva.[3,4] Dextromethorphan has also been suggested as a tool to investigate *N*-demethylation, an alternate metabolic pathway for this drug.[5]

1. Belec L, *et al.* Extensive oxidative metabolism of dextromethorphan in patients with almitrine neuropathy. *Br J Clin Pharmacol* 1989; 27: 387–90.
2. Streetman DS, *et al.* Dose dependency of dextromethorphan for cytochrome P450 2D6 (CYP2D6) phenotyping. *Clin Pharmacol Ther* 1999; 66: 535–41.
3. Hildebrand M, *et al.* Determination of dextromethorphan metabolizer phenotype in healthy volunteers. *Eur J Clin Pharmacol* 1989; 36: 315–18.
4. Hou Z-Y, *et al.* Salivary analysis for determination of dextromethorphan metabolic phenotype. *Clin Pharmacol Ther* 1991; 49: 410–19.
5. Jones DR, *et al.* Determination of cytochrome P450 3A4/5 activity in vivo with dextromethorphan N-demethylation. *Clin Pharmacol Ther* 1996; 60: 374–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Dextrotos; Romilar; *Austral.*: Benadryl Dry Forte; Bisolvon Dry; Robitussin Dry Cough Forte; Strepsils Cough Relief†; Vicks Formula 44 Dry Cough†; *Austria*: Tussastopp; Wick Formel 44 Husten-Pastillen; Wick Formel 44 Hustenstiller; *Belg.*: Actifed New; Balsoclase Dextromethorphan; Bisoltussin: Bronchosedal; Dexir; Humex†; Nortussine Mono; Romilar Antitussivum†; Soludril Antiussivum; Toux-San; Touxium Antitussivum; Tussipect†; Tusso Rhinathiol; Vicks Vaposyrup Antitussif; *Braz.*: Trimedal Tosse; *Canad.*: Balminil DM; Benylin DM-D-E-A Cold and Sinus; Benylin DM; Benylin Tickly Throat Cough; Bronchophan DM; Buckley's DM; Childrens Cough†; Cold and Flu-in-One; Cough Syrup DM; Delsym; DM Children's Cough Syrup; DM Cough Syrup; DM Sans Sucre; Dry Cough Syrup; Jack & Jill Thin Strips Cough†; Koffex DM; Neocitran Cough; Robitussin Childrens†; Robitussin DM CoughGels; Sedatuss DM; Sucrets Cough Control; Sucrets DM; Triaminic Cough; Triaminic DM; Triaminic Long Acting Cough; Vicks Custom Care Dry Cough; Vicks DayQuil Cough; Vicks Formula 44†; Vicks Pediatric Formula 44; *Chile*: Pectobronc; Tusminal; *China*: Bei Ke Er (倍克尔); Bei Tai (贝泰); Dekesi (德可思); Jiang Ke (降克); Kang Yu Deng Tong (康裕登通); Ke Le Er (可乐尔); Ke Li Ting (克立停); KeDi (可迪); Kening (科宁); Luo Shun (洛顺); Pusiran (普西兰); Rui Kai Ping (瑞凯平); Shu De (舒得); Shuang Hong Ling (双红灵); Xian Luo Ke (先罗可); Xiaomei (小眉); *Cz.*: Dr Rentschler Hustenstiller†; Humex Pro Deti; Robitussin Antitussicum; Robitussin Junior; Stopex; Tussidrill; *Denm.*: Dexofan; *Fin.*: Resilar; Rometor; *Fr.*: Atuxane; Capsyl†; Dexirt; Dextrocidine; Drill toux seche; Ergix Toux Seche; Euphonyl Toux Seche; Fluditec toux seche; Humex Toux Seche Dextromethorphane; Nodex; Pulmodexane; Tussidane; Tuxium; Vicks Toux Seche; *Ger.*: Hustenstiller; NeoTussan†; Silomat DMP; Wick Husten-Pastillen gegen Reizhusten mit Honig; Wick Husten-Sirup gegen Reizhusten mit Honig; *Gr.*: Vaposyrup; *Hong Kong*: Depan-F; Dexcophan†; Dextrome; Dextrophen†; Eifcof-G†; Pusiran; Robitussin DX; Robitussin Maximum Strength Cough†; Robitussin Paediatric Cough†; Tussils; Uni-DM†; *Hung.*: Drill†; Methort†; Rhinathiol; Robitussin Antitussicum; Robitussin Junior; Tussopront; *India*: Alex; Chericof; DM; Kofend-D; Kofgard; Lastuss; Lexcof; Omnitus; *Indon.*: Bisoltussin; Romilar; *Irl.*: Benylin Non-Drowsy Dry Cough; Delsym†; Robitussin Dry Cough; Robitussin Junior†; *Israel*: Kofli†; Kuflex DM; Tarodex; *Ital.*: Aricodiltosse; Bechilar; Bisolvon Tosse Sed; Bronchenolo Tosse; Bronchetab; Broncofama; Formitrol; Lisomucil Tosse Sedativo; Metorfan; Tossoral; Tussycalm; Vicks Tosse Pastiglie; Vicks Tosse Sedativo; *Malaysia*: Depan-F; Dexcophan†; Nospan; Pusiran; Tussidex Forte; Tussils; Upha Dextrophan; *Mex.*: Atassol; Athos; Balbek†; Balsedrina; Bekesina-S; Bekidiba Dex†; Bioquidan; Brocolan; Bromelip; Debequin; Dontuxin; Flex Metak; Jarabe Garde; Neo-Ulcoid; Protan; Quimofan; Romilar; Tosifan; *Neth.*: Bisoltussin; Dampo bij droge hoest†; Daro Retard; Darolan Hoestprikkeldempende†; Daromefan†; Dexal; Pectofree; Rami-Dextromethorfan†; Tussipect; Vicks Hoestsiroop; Vicks Hoesttabletten; *NZ*: Benadryl Dry Forte†; Robitussin DX; Strepsils Dry Cough; *Philipp.*: Cofles; Decormin; Dexof; Extendryl DM; Flemonex-DXM; Mytusan DM; Pulmodex; Strepsils Dry Cough; Streptuss; Suprekof DM†; *Pol.*: Acodin; Dexatussin; Robitussin Antitussicum; Robitussin Junior; Tussal Antitussicum; Tussidex; TussiDrill; *Port.*: Bisoltussin; Diacol; Drill Tosse Seca; Rhinathiol; Setustop; Tussilene; Vicks Pastilhas; Vicks Xarope Antitussico; *S.Afr.*: Benylin Dry Cough; Dilinct Dry Cough; *Singapore*: Beathorphan; Dexcophan; Metophan; Nospan; Pusiran; Robitussin Honey Cough; Tussidex; Tussils; *Spain*: Aquitos†; Bexatus; Bicasan; Bisolvon Antitusivo; Cinfatos; Couldetos; Formulatus; Prenatus†; Frituxil; Iniston Antitusivo; Laitos; Normotus; Notus; Novag Tuss; Parlatos; Pastillas Dr Andreu; Romilar; Serratos†; Streptuss†; Tip; Tusorama†; Tussidrill; *Switz.*: Bexine; Bexomed; Calmerphan-L; Calmesine; Dextro-Med; Emedrin N; Hicoseen N; Irotussin; Pulmofor; Tossa-X; Tussalpront†; Vicks Formule 44 Calmine†; Vicks Toux Seche; *Thai.*: A-Tussin; Antus; Cetussin; Cortuss; Dec; Depan-P†; Dex; Dextramet; Dextro-5; Dextrocough; Dextrodon; Dextromed; Dextropac; Dextroral; Dextrosia; Eifcof; Icolid Plus; Icolid; KB Dextro; Lohak; Manodextro; Methorphan; MLM-Dex†; Polydex; Potussan; Pusiran; Romilar; Strepsils Dry Cough; Throatsil Dex; Tusacdon; Tusco; Tussanyl; Tussils; *UAE*: Exedexe; Sedofan P†; *UK*: Adult Dry Cough; Benylin Dry Coughs Non-Drowsy; Dry Cough Syrup; Robitussin Dry Cough; Vicks Cough Lozenges with Honey; Vicks Cough Syrup with Honey for Dry Coughs; Vicks Vaposyrup for Dry Coughs; *Ukr.*: Daleron Cold 3 (Далерон Колд 3); *USA*: AeroTuss 12; Buckleys Cough; Creo-Terpin; Creomulsion; Delsym; DexAlone; Diabe-Tuss DM; ElixSure Childrens Cough; Hold DM; Little Colds Cough Formula; Long-Acting Cough Suppressant; PediaCare Childrens Long-Acting Cough; PediaCare Infants Long-Acting Cough; Robitussin Adult Lingering Cold Long-Acting Cough; Robitussin Children's Cough Long-Acting; Robitussin CoughGels; Robitussin Pediatric; Scot-Tussin Diabetes; Scot-Tussin DM Cough Chasers; Silphen DM; Simply Cough; Sucrets DM; Theraflu Cough; Triaminic Long Acting Cough; Trocal†; Vicks 44 Cough Relief; Vicks Nature Fusion Cough; *Venez.*: Libolar; Promedin; Tilodrin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Dextromethorphan Hydrobromide Syrup; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution.

Dimemorfan Phosphate *(rINNM)*

AT-17; Dimémorfane, Phosphate de; Dimemorfani Phosphas; Dimemorfano, fosfato de; Fosfato de dimemorfano; Димеморфана Фосфат.

(+)-3,9a-Dimethylmorphinan phosphate.

$C_{19}H_{32}NH_3PO_4$=353.4

CAS — 36309-01-0 (dimemorfan); 36304-84-4 (dimemorfan phosphate).

ATC — R05DA11.

ATC Vet — QR05DA11.

UNII — S203Y5Y1QP.

Pharmacopoeias. In *Jpn*.

Profile

Dimemorfan phosphate is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It is given orally in doses of 20 mg three or four times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Tusben; *Jpn*: Astomin; *Spain*: Dastosin.

Dimethoxanate Hydrochloride *(BANM, rINNM)*

Dimétoxanate, Chlorhydrate de; Dimethoxanati Hydrochloridum; Dimetoxanato, hidrocloruro de; Hidrocloruro de dimetoxanato; Диметоксаната Гидрохлорид.

2-(2-Dimethylaminoethoxy)ethyl 10-phenothiazine-10-carboxylate hydrochloride.

$C_{19}H_{22}N_2O_4S$,HCl=394.9

CAS — 477-93-0 (dimethoxanate); 518-63-8 (dimethoxanate hydrochloride).

ATC — R05DB28.

ATC Vet — QR05DB28.

UNII — N5165R31GJ.

Profile

Dimethoxanate hydrochloride is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It has been given orally in usual doses of 37.5 mg three or four times daily.

Dornase Alfa (BAN, USAN, rINN)

Deoxyribonuclease; Desoxyribonuclease; DNase I; Dornasa alfa; Dornasum Alfa; Domaz Alfa; rhDNase; Дорназа Альфа. Deoxyribonuclease I (human recombinant).

$C_{1321}H_{1995}N_{339}O_{396}S_9$=29250.0

CAS — 9003-98-9 (bovine deoxyribonuclease); 143831-71-4 (human deoxyribonuclease); 132053-08-8 (human deoxyribonuclease).

ATC — B06AA10; R05CB13.

ATC Vet — QB06AA10; QR05CB13.

UNII — 0BE71HM000 (bovine); 953A26OA1Y (human).

Description. Dornase alfa is a recombinant enzyme having the same amino acid sequence and glycosylation pattern as human deoxyribonuclease I.

Uses and Administration

Dornase alfa acts as a mucolytic by hydrolysing DNA that has accumulated in sputum from decaying neutrophils. It is used as a nebulised solution in patients with cystic fibrosis (below); in the UK its indication is limited to patients with a forced vital capacity (FVC) greater than 40% of predicted value and to patients over 5 years of age, but in the USA it may also be given for advanced disease (FVC less than 40%) and to younger children. The usual dose is 2500 units (2.5 mg) of dornase alfa given once daily via a jet nebuliser. This dose may be given twice daily to patients over 21 years of age.

Bovine deoxyribonuclease has been used similarly. It has also been used topically, often with fibrinolysin, as a debriding agent for inflammatory and infected lesions. Bovine deoxyribonuclease has also been given by injection.

Administration in children. Although in some countries dornase alfa is not recommended for use in children under 5 years of age (for details of doses, see Uses and Administration, above), a study[1] to assess the delivery of dornase alfa to the lungs of children with cystic fibrosis aged between 3 months and 5 years, showed that the amounts present in the lower airways were comparable to those in older children. It also appeared to be safe in these younger patients during the 2-week study period.

1. Wagener JS, *et al.* Aerosol delivery and safety of recombinant human deoxyribonuclease in young children with cystic fibrosis: a bronchoscopic study. *J Pediatr* 1998; 133: 486–91.

Asthma. There are reports of the use of dornase alfa to liquefy mucus plugs and relieve an attack of acute severe asthma (p. 1195.2) in children.[1-3] However, a randomised controlled study[4] found that adding a single dose of nebulised dornase alfa to standard emergency treatment has no benefits in children with moderate to severe acute asthma.

1. Greally P. Human recombinant DNase for mucus plugging in status asthmaticus. *Lancet* 1995; 346: 1423–4.
2. Patel A, *et al.* Intratracheal recombinant human deoxyribonuclease in acute life-threatening asthma refractory to conventional treatment. *Br J Anaesth* 2000; 84: 505–7.
3. Durward A, *et al.* Resolution of mucus plugging and atelectasis after intratracheal rhDNase therapy in a mechanically ventilated child with refractory status asthmaticus. *Crit Care Med* 2000; 28: 560–2.
4. Boogaard R, *et al.* Recombinant human deoxyribonuclease for the treatment of acute asthma in children. *Thorax* 2008; 63: 141–6.

Chronic obstructive pulmonary disease. A large phase III study in patients hospitalised for acute exacerbations of chronic bronchitis (p. 1199.1) was halted prematurely because of a non-significant trend to increased mortality in patients given dornase alfa.[1]

1. Hudson TJ. Dornase in treatment of chronic bronchitis. *Ann Pharmacother* 1996; 30: 674–5.

Cystic fibrosis. There is good evidence that inhalation therapy with dornase alfa can produce modest but useful improvement in lung function in some patients with cystic fibrosis (p. 177.2). Most studies have concentrated on patients with mild or moderate disease (forced vital capacity at least 40% of the predicted value) in whom FEV_1 and forced vital capacity have shown improvements generally of the order of 5 to 10%,[1-3] and in whom more prolonged therapy (24 weeks) has been shown to reduce the risk of exacerbations of respiratory infections, and hence the need for intravenous antibacterial therapy.[3] There is also evidence that benefit may occur in patients with more severe disease.[4] A systematic review[5] of studies concluded that there is evidence to show that dornase alfa therapy over a 1-month period is associated with improved lung function. Furthermore, a randomised, multicentre, placebo-controlled study[6] in children showed that dornase alfa maintained lung function and reduced the risk of exacerbations over a period of 96 weeks. However, only a minority of patients, perhaps about one-third,[7] benefit from the drug, and at present there is no way of identifying those who will respond other than by a therapeutic trial.[8,9]

Given the high cost of therapy, which is not entirely recouped by savings in acute care, there has been some controversy about the appropriate use of dornase alfa:[10-13] it seems to be generally felt that it should be reserved for specialist use in cystic fibrosis clinics, but that patients should not be denied a trial where appropriate. Most responders with mild to moderate impairment of lung function will show improvements within 2 weeks, although in more severely affected patients a 6-week trial is advocated.[8] A review of the use of dornase alfa in cystic fibrosis concluded that dosing on alternate days would be as effective as daily dosing, and would reduce costs and treatment time.[14]

1. Ramsey BW, *et al.* Efficacy and safety of short-term administration of aerosolized recombinant human deoxyribonuclease in patients with cystic fibrosis. *Am Rev Respir Dis* 1993; 148: 145–51.
2. Ranasinha C, *et al.* Efficacy and safety of short-term administration of aerosolised recombinant human DNase I in adults with stable stage cystic fibrosis. *Lancet* 1993; 342: 199–202.
3. Fuchs H, *et al.* Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med* 1994; 331: 637–42.
4. McCoy K, *et al.* Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest* 1996; 110: 889–95.
5. Jones AP, Wallis C. Dornase alpha for cystic fibrosis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2010 (accessed 17/05/10).
6. Quan JM, *et al.* A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis with mild lung function abnormalities. *J Pediatr* 2001; 139: 813–20.
7. Davis PB. Evolution of therapy for cystic fibrosis. *N Engl J Med* 1994; 331: 672–3.
8. Conway SP, Littlewood JM. rhDNase in cystic fibrosis. *Br J Hosp Med* 1997; 57: 371–2.
9. Ledson MJ, *et al.* Targeting of dornase alpha therapy in adult cystic fibrosis. *J R Soc Med* 1998; 91: 360–4.
10. Anonymous. Dornase alfa for cystic fibrosis. *Drug Ther Bull* 1995; 33: 15–16.
11. Spencer D, Weller P. Dornase-alfa for cystic fibrosis. *Lancet* 1995; 345: 1307.
12. Bush A, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; 310: 1533.
13. Robert G, *et al.* Dornase alfa for cystic fibrosis. *BMJ* 1995; 311: 813.
14. Suri R. The use of human deoxyribonuclease (rhDNase) in the management of cystic fibrosis. *BioDrugs* 2005; 19: 135–44.

Adverse Effects and Precautions

Common adverse effects with dornase alfa aerosol include pharyngitis, hoarseness of the voice, and chest pain. Occasionally laryngitis, conjunctivitis, and skin rashes and urticaria have been reported. There may be a transient decline in pulmonary function on beginning therapy with dornase alfa.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dornase alfa as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Pulmozyme; ***Austral.***: Pulmozyme; ***Austria***: Pulmozyme; ***Belg.***: Pulmozyme; ***Braz.***: Pulmozyme; ***Canad.***: Pulmozyme; ***Chile***: Viscozyme; ***Cz.***: Pulmozyme; ***Denm.***: Pulmozyme; ***Fin.***: Pulmozyme; ***Fr.***: Pulmozyme; ***Ger.***: Pulmozyme; ***Gr.***: Pulmozyme; ***Hung.***: Pulmozyme; ***Irl.***: Pulmozyme; ***Israel***: Pulmozyme; ***Ital.***: Pulmozyme; ***Jpn***: Pulmozyme; ***Mex.***: DNSM; Pulmozyme; ***Neth.***: Pulmozyme; ***Norw.***: Pulmozyme; ***NZ***: Pulmozyme; ***Pol.***: Pulmozyme; ***Port.***: Pulmozyme; ***Rus.***: Pulmozyme (Пульмозим); ***S.Afr.***: Pulmozyme; ***Spain***: Pulmozyme; ***Swed.***: Pulmozyme; ***Switz.***: Pulmozyme; ***Turk.***: Pulmozyme; ***UK***: Pulmozyme; ***Ukr.***: Pulmozyme (Пульмозим); ***USA***: Pulmozyme.

Multi-ingredient Preparations. ***Arg.***: Clorfibrase; ***Austria***: Fibrolan; ***Braz.***: Cauterex; Fibrabene; Fibrase; Fibrinase c/Cloranfenicol; Gino Cauterex; Gino Fibrase; ***Chile***: Elase; ***Cz.***: Fibrolan†; ***Fr.***: Elase; ***Hung.***: Fibrolan; ***Malaysia***: Elase; ***Mex.***: Fibrase SA; Fibrase; Ridasa; ***Pol.***: Fibrolan; ***Switz.***: Fibrolan.

Dropropizine (BAN, rINN)

Dropropitsiini; Dropropizin; Dropropizina; Dropropizinum; UCB-1967; Дропропизин.

3-(4-Phenylpiperazin-1-yl)propane-1,2-diol.

$C_{13}H_{20}N_2O_2$=236.3

CAS — 17692-31-8.

ATC — R05DB19.

ATC Vet — QR05DB19.

UNII — U0K8WHL37U.

Levodropropizine (BAN, rINN)

DF-526; Levdropropizine; Levodropropitsiini; Levodropropizin; Levodropropizina; Levodropropizinas; Lévodropropizine; Levodropropizinum; Леводропропизин.

The (-)-(*S*)-isomer of dropropizine.

$C_{13}H_{20}N_2O_2$=236.3

CAS — 99291-25-5.

ATC — R05DB27.

ATC Vet — QR05DB27.

UNII — 3O31P6T4G3.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Levodropropizine). A white or almost white powder. Slightly soluble in water and in alcohol; freely soluble in dilute acetic acid and in methyl alcohol. A 2.5% solution in water has a pH of 9.2 to 10.2. Protect from light.

Profile

Dropropizine is a cough suppressant reported to have a peripheral action in non-productive cough (p. 1651.2). It is given orally usually in a dose of 30 mg three or four times daily. Levodropropizine, the (-)-(*S*)-isomer of dropropizine, is claimed to produce fewer CNS effects and is used similarly in an oral dose of 60 mg up to three times daily.

References.

1. Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough: comparison with dextromethorphan. *Pulm Pharmacol Ther* 1997; 10: 89–96.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Perlatos; ***Belg.***: Catabex; Levotuss; ***Braz.***: Antux; Atossion; Ecos; Eritos; Flextoss; Neotoss; Percof; Tussiflex D; Vibral; Vibrazin; Zyplo; ***Chile***: Broncard; Broncatox; ***China***: JiShu (及舒); Kao Fu Ting (考孚亭); Ke Chang (可畅); Ke Li Yu (可利愈); Run Hui (润汇); Shu Chang (抒畅); Zuo Pai Xin (佐派欣); ***Cz.***: Ditustat; Levopront; ***Ger.***: Larylin Husten-Stiller; Quimbo; ***Gr.***: Dropavix; Levotuss; ***Hong Kong***: Bronal; ***Hung.***: Levopront; ***Indon.***: Levopront; ***Ital.***: Actiribex; Danka; Domutussina; Levotuss; Salvituss; Tau-Tux; ***Mex.***: Kastovin; Levocof; Troferit; Velatuss; Zyplo; ***Neth.***: Levotuss; ***Philipp.***: Levopront; ***Pol.***: Levopront; ***Port.***: Catabina; Levotuss; ***Rus.***: Levopront (Левопронт); ***Spain***: Levotuss; Tautoss; ***Thai.***: Bronal; Ivorin; Levopront; ***Turk.***: Lavenil; Levopront; Pulmorest; ***Venez.***: Antux; Levopront.

Multi-ingredient Preparations. ***Braz.***: Notuss; ***Ital.***: Actiribexen; Elisir Terpina; Guaiacalcium Complex; Tiocalmina; Tussamag Complex; ***Mex.***: Dizolvin-Flux.

Elecampane

Ala; Alant; Aunée; Énula; Énula campana; Helenio; Inula; Ínula; Девясил Высокий.

CAS — 97676-35-2 (elecampane oil).

UNII — 3VD070DG5G (Inula helenium); E55SMD6DA8 (Inula helenium root); VN35VNS0OO (Inula helenium root oil).

Pharmacopoeias. In *Chin.* (which also includes various other species of *Inula*) and *Fr.*

Profile

Elecampane is the root of *Inula helenium* (Compositae). It has been used in herbal preparations for the treatment of cough for its supposed expectorant and cough suppressant properties. It is also used as a flavouring in foods and alcoholic beverages.

Elecampane contains sesquiterpene lactones including alantolactone (alant camphor; elecampane camphor; inula camphor; helenin), which was formerly used in the treatment of worm infections, and has also been an ingredient of some cough preparations.

Elecampane oil has been used in aromatherapy.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Austral.***: HRF; ResCo; ***Austria***: Brust- und Hustentee St Severin; Klosterfrau Melissengeist; Pervivo; ***Canad.***: Herbal Cough Syrup†; Honey Blend Herbal Cough Syrup; ***Cz.***: Klosterfrau Melisana; Species Cholagogae Planta†; ***Fr.***: Mediflor Digestive No 3; ***Ger.***: Klosterfrau Melissengeist; ***Hung.***: Antipoll; Bittner; Klosterfrau Melisana; ***Pol.***: Pectosol; Pervivo; ***Rus.***: Original Grosser Bittner Balsam (Оригинальный Большой Бальзам Биттнера); Sodecor (Содекор); ***S.Afr.***: Wonderkroonessens; ***Switz.***: Hederix; Padmed Laxan; ***UK***: Catarrh-eeze; Cough Soother Herbal Syrup; Cough-eeze; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Vegetable Cough Remover; ***Ukr.***: Pectolvan Phyto (Пектолван Фито).

Homoeopathic Preparations. ***Ger.***: Drosera-Weliplex†; ***Neth.***: Drosinula.

Ephedra ⊗

Efedra; Ma-huang; Эфедра хвощевая (*Ephedra equisetina*); Хвойник.

UNII — 2E31ONF9M5 (Ephedra intermedia stem); 5SL3XLO37E (Ephedra sinica stem).

Pharmacopoeias. In *Chin., Eur.*, (see p. vii) *Ger.*, and *Jpn.*

Chin. also includes the roots of *Ephedra sinica* or *E. intermedia.*

Ph. Eur. 8: (Ephedra Herb); Ephedrae Herba. The dried herbaceous stem of *Ephedra sinica, E. intermedia,* or *E. equisetina.* It contains a minimum of 1% of ephedrine.

Profile

Ephedra consists of the dried young branches of *Ephedra sinica, E. equisetina,* and *E. gerardiana* (including *E. nebrodensis*) (Ephedraceae), containing not less than 1.25% of alkaloids, calculated as ephedrine.

The action of ephedra is due to the presence of ephedrine (below) and pseudoephedrine (p. 1676.1). It has been used chiefly as a source of these alkaloids. The FDA states that ephedra-containing dietary supplements are unsafe and the sale of these products is banned in the USA. Other countries have also banned the sale of ephedra-containing dietary supplements.

For reference to the adverse effects of herbal products containing ephedra, see Abuse, under Ephedrine, p. 1664.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Formula S/E†; Sinueaze†.

Multi-ingredient Preparations. *Ger.*: Cefadrin†; *Hong Kong*: Sessoforte†; *Jpn*: Bofutsushosan; Colgen Maoto; Eppikajutsuto; Gokoto; Goshakusan; Kakkonto; Kakkontokasenkyushin'i; Makyokansekito; Makyoyokukanto; Maobushisaishinto; Maoto; Shimpito; Shoseiryuto; Yokuininto.

Homoeopathic Preparations. *Fr.*: Santaherba; *Rus.*: Sambucus-Plus (Самбукус-Плюс).

Ephedrine *(BAN)* ⊗

Efedriini; Efedrin; Efedrina; Efedrinas; Ephedrina; (-)-Ephedrine; Éphédrine; Ephedrinum; Эфедрин.

(1*R*,2*S*)-2-Methylamino-1-phenylpropan-1-ol.

$C_{10}H_{15}NO$=165.2

CAS — 299-42-3 (anhydrous ephedrine); 50906-05-3 (ephedrine hemihydrate).

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QG04BX90; QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — GN83C131XS.

Description. Ephedrine is an alkaloid obtained from species of *Ephedra,* or prepared synthetically. It may exist in a hemihydrate form or as the anhydrous substance.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of ephedrine:

Trucker's Speed.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *US*, which have specifications, in either the same monograph or in separate monographs, for the anhydrous form and for the hemihydrate.

Ph. Eur. 8: (Ephedrine, Anhydrous). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 36 degrees. Protect from light.

Ph. Eur. 8: (Ephedrine Hemihydrate; Ephedrine BP 2014). A white or almost white, crystalline powder or colourless crystals. Soluble in water; very soluble in alcohol. It melts at about 42 degrees, determined without previous drying. Protect from light.

USP 36: (Ephedrine). It is anhydrous or contains not more than one-half molecule of water of hydration. It is an unctuous, practically colourless solid or white crystals or granules. It gradually decomposes on exposure to light. M.p. between 33 degrees and 40 degrees, the variability being the result of differences in the moisture content, anhydrous ephedrine having a lower melting-point than the hemihydrate. Soluble 1 in 20 of water and 1 in 0.2 of alcohol; soluble in chloroform and in ether; moderately and slowly soluble in liquid paraffin, the solution becoming turbid if the ephedrine contains more than about 1% of water. Its solutions are alkaline to litmus. Store in airtight containers at a temperature not exceeding 8 degrees. Protect from light.

Ephedrine Hydrochloride *(BANM)* ⊗

Efedriinihydrokloridi; Efedrin Hidroklorür; Efedrin hydrochlorid; Efedrina, hidrocloruro de; Efedrin-hidroklorid; Efedrinhydroklorid; Efedrino hidrochloridas; Efedryny chlorowodorek; Ephedrinae Hydrochloridum; Éphédrine, chlorhydrate d'; Ephedrine Chloride; Ephedrinhydrochlorid; Ephedrini Hydrochloridum; Ephedrinium Chloratum; L-Ephedrinum Hydrochloricum; Эфедрина Гидрохлорид.

$C_{10}H_{15}NO.HCl$=201.7

CAS — 50-98-6.

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — NLJ6390P1Z.

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.*

Ph. Eur. 8: (Ephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol. It melts at about 219 degrees. Protect from light.

USP 36: (Ephedrine Hydrochloride). Fine, white, odourless crystals or powder. Soluble 1 in 3 of water and 1 in 14 of alcohol; insoluble in ether. Protect from light.

Ephedrine Sulfate *(BANM)* ⊗

Efedrina, sulfato de; Ephedrine Sulphate; Эфедрина Сульфат.

$(C_{10}H_{15}NO)_2.H_2SO_4$=428.5

CAS — 134-72-5.

ATC — C01CA26; R01AA03; R01AB05; S01FB02.

ATC Vet — QR01AA03; QR01AB05; QR03CA02; QS01FB02.

UNII — U6X61U5ZEG.

Pharmacopoeias. In *Int.* and *US.*

USP 36: (Ephedrine Sulfate). Fine, white, odourless crystals or powder. It darkens on exposure to light. Soluble 1 in 1.3 of water and 1 in 90 of alcohol. Protect from light.

Racephedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

dl-Ephedrine Hydrochloride; *dl*-Ephedrinium Chloride; Efedriinihydrokloridi, raseeminen; Efedrinhydroklorid, racemisk; Efedrino (raceminio) hidrochloridas; Éphédrine (chlorhydrate d') racémique; Ephedrini racemici hydrochloridum; Hidrocloruro de racefedrina; Racém efedrin-hidroklorid; Racemic Ephedrine Hydrochloride; Racéphédrine, Chlorhydrate de; Racephedrini Hydrochloridum; Рацефедрина Гидрохлорид.

(±)-2-Methylamino-1-phenylpropan-1-ol hydrochloride.

$C_{10}H_{15}NO.HCl$=201.7

CAS — 90-81-3 (racephedrine); 134-71-4 (racephedrine hydrochloride).

UNII — 43SK4LAO7D.

Pharmacopoeias. In *Eur.*

Ph. Eur. 8: (Ephedrine Hydrochloride, Racemic; Racephedrine Hydrochloride BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; soluble in alcohol; practically insoluble in ether. It melts at about 188 degrees. Protect from light.

Uses and Administration

Ephedrine is a sympathomimetic (p. 1507.3) with direct and indirect effects on adrenergic receptors. It has alpha- and beta-adrenergic activity and has pronounced stimulating effects on the CNS. It has a more prolonged though less potent action than adrenaline. In therapeutic doses it raises the blood pressure by increasing cardiac output and also by inducing peripheral vasoconstriction. Tachycardia may occur but is less frequent than with adrenaline. Ephedrine also causes bronchodilatation, reduces intestinal tone and motility, relaxes the bladder wall while contracting the sphincter muscle but relaxes the detrusor muscle of the bladder and usually reduces the activity of the uterus. It has a stimulant action on the respiratory centre. It dilates the pupil but does not affect the light reflexes. After ephedrine has been used for a short while, tachyphylaxis may develop.

Ephedrine salts are used, either alone or in combination preparations, in the symptomatic relief of nasal congestion (p. 1652.1). They may be given orally, or topically as nasal drops or sprays. Ephedrine salts have sometimes been used in motion sickness in combination preparations with hyoscine or an antihistamine and have been tried for postoperative nausea and vomiting (p. 1811.3).

Ephedrine salts have been given parenterally to combat a fall in blood pressure during spinal or epidural anaesthesia (below). Ephedrine is of little value in hypotensive crises produced by shock, circulatory collapse, or haemorrhage. It is no longer generally advocated for orthostatic hypotension.

Ephedrine salts have been used as bronchodilators, but the more beta$_2$-selective sympathomimetics, such as salbutamol, are now preferred.

Other uses of ephedrine salts include diabetic neuropathic oedema, in which they may provide marked relief. They have also been used in micturition disorders.

Nasal drops or sprays usually containing ephedrine 0.5 or 1% are used in the treatment of **nasal congestion.** Ephedrine salts have also been given by oral inhalation.

To reverse **hypotension** induced by spinal or epidural anaesthesia, a solution containing ephedrine hydrochloride 3 mg/mL is given by slow intravenous injection in doses of 3 to 6 mg (or at most 9 mg) repeated every 3 to 4 minutes as required; the maximum total dose is 30 mg. Ephedrine salts have also been given by intramuscular or subcutaneous injection.

The *BNF* suggests an oral dose of 30 to 60 mg of ephedrine hydrochloride three times daily in the treatment of **diabetic neuropathic oedema.**

Several other salts of ephedrine have been given including the camsilate, the levulinate, the tannate, and the thiocyanate. Racephedrine hydrochloride has also been used.

For doses in children, see below.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including ephedrine) should be used with caution in children and generally avoided in young children, for details see p. 1651.2. The *BNFC* suggests that ephedrine nasal drops may be used in children aged 6 years and over for the short-term treatment of severe **nasal congestion** that has not responded to sodium chloride nasal drops or inhalation of warm moist air. Nasal drops containing ephedrine hydrochloride 0.5% may be instilled into each nostril up to 3 or 4 times daily for a maximum of 5 days in children aged 6 to 12 years or 7 days in those over 12 years.

Ephedrine is rarely needed in children for reversal of **hypotension** induced by spinal or epidural anaesthesia, but if it is used the *BNFC* suggests the following doses of a solution containing ephedrine hydrochloride 3 mg/mL, given by slow intravenous injection via a central line:

- 1 to 12 years: 500 to 750 micrograms/kg or 17 to 25 mg/m^2 every 3 to 4 minutes according to response up to a maximum total dose of 30 mg
- 12 to 18 years: 3 to 7.5 mg (maximum 9 mg) repeated every 3 to 4 minutes according to response up to a maximum total dose of 30 mg

Congenital myasthenia. Ephedrine has been shown to be of benefit in certain types of congenital myasthenia (p. 685.1).

Micturition disorders. Ephedrine salts have been used in nocturnal enuresis, although other treatments are usually preferred, and have been tried in patients with stress incontinence but the value of such treatment is not clear.

Spinal anaesthesia. Parenteral sympathomimetics such as ephedrine and phenylephrine have been advocated for the correction of hypotension associated with local anaesthesia. The risk of hypotension with spinal or epidural block is greater than many other forms of nerve block (see Adverse Effects of Central Block, p. 1978.1). Ephedrine has been used[1,2] although not always successfully[3] for the correction of such hypotension. It has also been used prophylactically,[4,5] although prophylactic use during labour has been associated with fetal tachycardia,[5] and adequate hydration of the patient beforehand is more important in minimising hypotension.

1. Hall PA, *et al.* Spinal anaesthesia for Caesarean section: comparison of infusions of phenylephrine and ephedrine. *Br J Anaesth* 1994; **73**: 471–4.
2. Thomas DG, *et al.* Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anaesthesia for Caesarean section. *Br J Anaesth* 1996; **76**: 61–5.
3. Critchley LAH, *et al.* Hypotension during subarachnoid anaesthesia: haemodynamic effects of ephedrine. *Br J Anaesth* 1995; **74**: 373–8.
4. Stemlo J-E, *et al.* Prophylactic im ephedrine in bupivacaine spinal anaesthesia. *Br J Anaesth* 1995; **74**: 517–20.
5. Cleary-Goldman J, *et al.* Prophylactic ephedrine and combined spinal epidural: maternal blood pressure and fetal heart rate patterns. *Obstet Gynecol* 2005; **106**: 466–72.

Adverse Effects

As for Sympathomimetics, p. 1508.2. Ephedrine has both alpha- and beta-agonist effects and its commonest adverse effects are tachycardia, anxiety, restlessness, and insomnia. Tremor, dry mouth, impaired circulation to the extremities, hypertension, and cardiac arrhythmias may also occur.

Ephedrine may be used in labour to maintain blood pressure during spinal anaesthesia but can cause fetal tachycardia.

Paranoid psychosis, delusions, and hallucinations may also follow ephedrine overdosage. Prolonged use has no cumulative effect, but tolerance with dependence has been reported.

For a discussion of the toxicity reported from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, see Abuse, below.

Precautions

As for Sympathomimetics, p. 1508.3. Ephedrine should be given with care to patients with hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, renal impairment, or angle-closure glaucoma. In patients with prostatic enlargement, ephedrine may increase difficulty with micturition.

Irritability and disturbed sleep have been reported in breast-fed infants.

Abuse. Although illicit use of ephedrine is mainly in the manufacture of street stimulants such as metamfetamine (p. 2324.2), there is increasing evidence of the abuse of ephedrine preparations in some countries,[1] and the public health and social problems associated with its abuse appear to be significant, particularly in certain African countries. Ephedrine is also sold as a street substitute for 'Ecstasy' (Methylenedioxymethamfetamine, p. 2325.2).

Adverse effects reported with illicit ephedrine use include cardiovascular toxicity[2,3] and chest pain.[4]

There is controversy over the abuse liability of over-the-counter (OTC) stimulants such as ephedrine:[5] some studies have indicated that ephedrine is, overall, a relatively weak reinforcer whereas others have suggested that the abuse potential may be high. Examination of the characteristics of 5 patients who had been taking ephedrine-containing OTC preparations in high doses for periods ranging from 8 months to 2 years, emphasised the reinforcing and, therefore, addictive potential of ephedrine; similar observations were made for 2 patients who had ingested phenylpropanolamine long term, combined with pseudoephedrine in one of these cases. The authors suggested that, for most people, OTC preparations containing weaker sympathomimetics will not be reinforcing at the recommended doses. However, these cases strengthen the research findings that high-dose use of an OTC stimulant increases its potency, and thus its effects become more like amfetamine (p. 2316.1).

Toxicity has also been reported[6-8] from the self-administration of ephedrine-containing dietary supplements or herbal stimulants, usually based on ephedra (ma-huang) and marketed for a variety of purposes including weight loss and as an alternative to illegal drugs of abuse. Not all cases of ephedrine toxicity have arisen as a result of overt abuse but rather because of inadequate labelling of content and dosage instructions on some unlicensed products. A small study found that combinations of herbal caffeine and ephedra alkaloids taken in recommended amounts resulted in plasma ephedrine concentrations that exceeded the usual therapeutic range. Significant increases occurred in blood pressure and heart rate, and unfavourable effects on glucose and potassium homoeostasis were noted.[9] The use of ephedra-containing dietary supplements is now banned in the USA and some other countries.

Adverse effects from ingestion of ephedrine-containing OTC preparations, including herbal products (usually in high doses and/or long term) have included coronary artery thrombosis,[10] myocardial infarction, seizures,[11] psychotic reactions,[12] nephrolithiasis,[13-15] and myocarditis;[16] some fatalities have been reported. Frank dependence has been reported in female weightlifters following long-term use of high doses.[17]

For a report of urinary calculi developing in a patient who had ingested a preparation containing guaifenesin and ephedrine, see Abuse, under Guaifenesin, p. 1666.3.

1. WHO. Recommendations from the Expert Committee on Drug Dependence. *WHO Drug Inf* 1998; 12: 227–9.
2. Cockings JGL, Brown MA. Ephedrine abuse causing acute myocardial infarction. *Med J Aust* 1997; 167: 199–200.
3. Zahn KA, *et al.* Cardiovascular toxicity after ingestion of "herbal ecstacy" [sic]. *J Emerg Med* 1999; 17: 289–91.
4. James LP, *et al.* Sympathomimetic drug use in adolescents presenting to a pediatric emergency department with chest pain. *J Toxicol Clin Toxicol* 1998; 36: 321–8.
5. Tinsley JA, Watkins DD. Over-the-counter stimulants: abuse and addiction. *Mayo Clin Proc* 1998; 73: 977–82.
6. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; 343: 1833–8.
7. Dennehy CE, *et al.* Dietary supplement-related adverse events reported to the California Poison Control System. *Am J Health-Syst Pharm* 2005; 62: 1476–82.
8. Samenuk D, *et al.* Adverse cardiovascular events temporally associated with ma huang, an herbal source of ephedrine. *Mayo Clin Proc* 2002; 77: 12–16.
9. Haller CA, *et al.* Short-term metabolic and hemodynamic effects of ephedra and guarana combinations. *Clin Pharmacol Ther* 2005; 77: 560–71.
10. Sola S, *et al.* Coronary dissection and thrombosis after ingestion of ephedra. *Am J Med* 2004; 116: 645–6.
11. Anonymous. Adverse events associated with ephedrine-containing products—Texas, December 1993-September 1995. *JAMA* 1996; 276: 1711–12.
12. Doyle H, Kargin M. Herbal stimulant containing ephedrine has also caused psychosis. *BMJ* 1996; 313: 756.
13. Powell T, *et al.* Ma-huang strikes again: ephedrine nephrolithiasis. *Am J Kidney Dis* 1998; 32: 153–9.
14. Blau JJ. Ephedrine nephrolithiasis associated with chronic ephedrine abuse. *J Urol (Baltimore)* 1998; 160: 825.
15. Hoffman N, *et al.* Resolution of ephedrine stones with dissolution therapy. *Urology* 2003; 61: 1035.
16. Zaacks SM, *et al.* Hypersensitivity myocarditis associated with ephedra use. *J Toxicol Clin Toxicol* 1999; 37: 485–9.
17. Gruber AJ, Pope HG. Ephedrine abuse among 36 female weightlifters. *Am J Addict* 1998; 7: 256–61.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ephedrine, when used as a bronchodilator, as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Ephedrine has direct and indirect actions and may cause a hypertensive crisis in patients receiving an MAOI (including a RIMA); the possibility of such an interaction after intranasal use of ephedrine should also be borne in mind. See also under Phenelzine (p. 445.1) and Moclobemide (p. 438.1). Since ephedrine has both alpha- and beta-agonist properties it should be avoided or used with care in patients undergoing anaesthesia with cyclopropane, halothane, or other volatile anaesthetics. An increased risk of arrhythmias may occur if given to patients receiving cardiac glycosides, quinidine, or tricyclic antidepressants, and there is an increased risk of vasoconstrictor or pressor effects in patients receiving ergot alkaloids or oxytocin. The rate of metabolism of some other drugs is increased by ephedrine. For mention of the potential additive stimulant effects seen with caffeine and ephedrine, see Sympathomimetics, under Caffeine, p. 1206.2. For the effect of ephedrine on histamine given exogenously, see p. 2525.3.

Pharmacokinetics

Ephedrine is readily and completely absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine, with small amounts of metabolites produced by hepatic metabolism. Ephedrine has been variously reported to have a plasma half-life ranging from 3 to 6 hours depending on urinary pH; elimination is enhanced and half-life accordingly shorter in acid urine.

References.

1. Welling PG, *et al.* Urinary excretion of ephedrine in man without pH control following oral administration of three commercial ephedrine sulfate preparations. *J Pharm Sci* 1971; 60: 1629–34.
2. Sever PS, *et al.* The metabolism of (-)-ephedrine in man. *Eur J Clin Pharmacol* 1975; 9: 193–8.
3. Pickup ME, *et al.* The pharmacokinetics of ephedrine after oral dosage in asthmatics receiving acute and chronic treatment. *Br J Clin Pharmacol* 1976; 3: 123–34.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Muchan; *Belg.*: Ephedronguent†; *Braz.*: Unifedrine; *Chile*: Efedrosan†; *Gr.*: Neo Rhinovit; Rhinolex; *Hong Kong*: Efmol†; *Hung.*: Epheri†; *India*: Efipres: *Mex.*: Tendrin†; *Pol.*: Efrinol: *Port.*: Spinefe: *Turk.*: Rinitalmit†; *UK*: CAM; *USA*: Kondon's Nasal; *Venez.*: Colirio Iris.

Multi-ingredient Preparations. *Arg.*: Amiorel Compuesto; Aqua Lent Colirio; Bideon Free; Bisolvon Compositum; Clarisoft; Coliria; Efodil; Exudrol; Fadatos; Irix Clasico; Kalopsis; Neoefodil; No-Tos Adultos; Quemicetina Nasal Compuesta; Sintebron; Usualix; Vislus; *Austria*: Coldargan; Famel cum Ephedrin†; Helopyrin; Novipec†; Pilka Forte; Piniment; Spirbon†; Wick Erkaltungs-Saft fur die Nacht†; Wick Erkaltungssirup fur die Nacht; *Belg.*: Argyrophedrine†; Endrine Doux; Endrine; *Braz.*: Beclase†; Franol; Inhalante Yatropan; Marax; Rinisone; Tonaton; *Canad.*: Madame Pearl's Cough Syrup; Rhino-Vaccin†; *Chile*: Broncodeina; Pulmagol; *China*: Cofetol (臭亭); Compound Codeine (复方待因); Fufang Dan An Pian (复方胆氢片); Libang Zhikelu (联邦止咳露); *Cz.*: Mukoseptonex E; Tussilen†; *Fin.*: Codesan Comp; Sir. Ephedrin; *Fr.*: Caustinerf Arsenical; Devitasol Arsenical†; Osmotol; Otylol; Rhinamide; Rhino-Sulfuryl; Transmer†; Yranicid Arsenical; *Ger.*: Wick Medinait fur die Nacht; *Gr.*: Evex; Neo-Bronchoton-R; Otil; Sival-B; Toryl; Torylet; *Hong Kong*: Against Cough†; Amiton†; Antihist BC Expectorant†; Antipect†; Co-Epherine†; Coci-Fedra-C†; Coryl†; DEC†; Decofam Cough; Dhasedyl; Ephecol†; Ephedyl-DM†; Ephedyl†; Ephendyln†; Fendil†; Fendyl; Pritussin†; Marsedyl†; Methor-Co†; Methorsedyl; Metoplex; Neo-Tussin†; P.E. D.†; PEC; Pecolin†; Phensedyn; Promethazine Compound Linctus†; Prosedyl†; Sedral†; Sedylin†; Uni-Ramine CE; Uni-Theodal†; *Hung.*: Coderetta N; Coderit N; Coldargan†; Hemorid; Hemorid; *India*: Alergin; Asmapax; Bronolax; Cadiphylate; Cafona-E; Codoric; Cofton SP; Cortasthma; Dericip Plus; Elixir Efelin; Endrine Mild; Endrine; Gocold; Jiffy; Kufma; Marax; Mulitmix; Multimix; Multimix; Osdoril; *Indon.*: Asmadex; Asmano; Asmasolon; Asthma Soho; Bronchitin; Cold Cap; Ersylan; Kafsir; Koffex for Children; Mixadin; Neo Napacin†; Oskadryl; Phenadex; Poncolin D; Poncolin; Prinasma†; Theochodil; Thymcal; *Israel*: Perrussol; Proaf†; To-Care; Tucare; Tussophedrine NF; Tussosedan†; *Ital.*: Argotone Rino; Deltarinolo; Flenamina; Pasta Arsenicale; Rinovit; *Malaysia*: Asthma; Cofnil-N†; Dexcophan Cough†; Dhasedyl DM; Diprodin; Phensedyl Dry Cough; *Mex.*: Alfan†; Broncofedrina; Coderit; Jarabe de Capulin†; Paliatil; *Pol.*: Rubital Compositum; Syrop Prawoslazowy Zlozony; Tussipect; Tussipect; *Port.*: Anti-Asmatico†; Ipesandrine†; Mebocatuss; Sedotusse†; *Rus.*: Bronchitussin (Бронхитуссен); Bronchocin (Бронхоцин); Broncholytin (Бронхолитин); Bronchoton (Бронхотон); Insanovin (Инсановин); Solutan (Солутан)†; Theophedrinum-N (Теофедрин-Н); *S.Afr.*: Brunacod†; Codef†; Colcleer; Corbar; Coughcod†; Dequa-Coff; Docsed†; Flusin†; Genasma†; Grippon†; Lenazine Forte; Linctodyl†; Natrophylline Compound†; Oto-Phen Forte†; Phensedyl; Repasma†; Sinucon; Sinuend; Vicks Medinite†; *Singapore*: Alcough; Ancolin; Anti-phlegm; Beacons Cough; Brecolin; Chlorsedyl; Cophadyl-E; Coughlax; Decofam Cough; Dexcophan Cough Linctus Plus; Dhasedyl DM; Dhasedyl; Diprodin; Ephedyl DM; Ephedyl; Pico's Children's Cough; Pico's Cough; PO-V-SU; Polins Cough; Promedyl; Robinson Cough; Sedilix; Semerin; SP-Brom; Sunamine; Sunny Children Cough; Sunsedyl; Veelanz's Cough Syrup; Vyling Anti-Cough Menthol; Williams Cough; *Spain*: Bisolvon Compositum†; Brota Rectal Balsamico†; Cilinafosal Dihidroestreptomicina†; Cilinafosal Hidrocortisona†; Cilinafosal Neomicina†; Cilinafosal†; Fludren†; Hemoal; Kanafosal Predni†; Kanafosal†; Medinait; Pazbronquial; Tabletas Quimpe†; Vitavox†; Voxfor†; *Swed.*: Lepheton; Lergigan comp; Mollipect; *Switz.*: Demo Elixir pectoral N†; Haemolan†; Kemeol†; Pastilles pectorales du Dr. Welti; Pectocalmine N; Sano Tuss; Sanotussin; Vicks Medinait; *Turk.*: Antibeksin; Artu; Brodil; Broksin; Defeks; Dorfan; Eupnase; Fenasthma; Fenokodin†; Hemoralgine; Latusin†; Neo Sedeks; Neofedrin; Pedrin; Pektodin†; Penikin†; Pereks; Radycodin; Radyokodin; Sulfarhin; *UAE*: Codaphed Plus; Codaphed; *UK*: Do-Do ChestEze; Dolvan; Haymine; Noradran; Paranorm; *Ukr.*: Bronchobru (Бронхобрю); Broncholytin (Бронхолитин); *USA*: Broncholate†; Bronkaid Dual Action†; Bronkotuss Expectorant; Hydrophed; KIE; Marax; Pazo; Primatene; Quadrinal; Quelidrine; Rentamine Pediatric; Rynatuss†; Tedrigen; Theodrine; Theomax DF; Tri-Tannate Plus Pediatric; Tuss-Tan; *Venez.*: Amodion; Pi-Fedrin; Pidrol; Tabonuco.

Homoeopathic Preparations. *Chile*: Ikoplex No 3.

Pharmacopoeial Preparations

BP 2014: Ephedrine Elixir; Ephedrine Hydrochloride Tablets; Ephedrine Injection; Ephedrine Nasal Drops;

USP 36: Ephedrine Sulfate Capsules; Ephedrine Sulfate Injection; Ephedrine Sulfate Nasal Solution; Ephedrine Sulfate Syrup; Theophylline, Ephedrine Hydrochloride, and Phenobarbital Tablets.

Eprazinone Hydrochloride *(rINNM)*

CE-746; Eprazinona, hidrocloruro de; Éprazinone, Chlorhydrate d'; Eprazinoni Hydrochloridum; Hidrocloruro de eprazinona; Эпразинона Гидрохлорид.

3-[4-(β-Ethoxyphenethyl)piperazin-1-yl]-2-methylpropiophenone dihydrochloride.

$C_{24}H_{32}N_2O_2.2HCl$=453.4

CAS — 10402-90-1 (eprazinone); 10402-53-6 (eprazinone hydrochloride).

ATC — R05CB04.

ATC Vet — QR05CB04.

UNII — 394X1L8I9Y.

Profile

Eprazinone hydrochloride has been variously described as having mucolytic or expectorant properties as well as a direct relaxant action on bronchial smooth muscle. It is used for cough (p. 1651.2) and is given in oral doses of 50 to 100 mg three times daily. It has also been given rectally.

Effects on the skin. Skin eruptions have been associated with the oral use of eprazinone.[1,2]

1. Faber M, *et al.* Eprazinonexanthem mit subkornealer Pustelbildung. *Hautarzt* 1984; 35: 200–3.
2. Tanabe K, *et al.* Non-pigmented fixed drug eruption induced by eprazinone hydrochloride. *Dermatol Online J* 2005; 11: 25.

Overdosage. Symptoms in two 22-month-old children who received an overdose of 800 mg of eprazinone included somnolence, ataxia, and seizures.[1]

1. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; 32: 504–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Isilung†; *Fr.*: Mucitux; *Jpn*: Resplen.

Eprozinol Hydrochloride *(rINNM)*

Éprozinol, Chlorhydrate d'; Eprozinoli Hydrochloridum; Hidrocloruro de eprozinol; Эпрозинола Гидрохлорид.
3-[4-(β-Methoxyphenethyl)piperazin-1-yl]-1-phenylpropan-1-ol dihydrochloride.
$C_{22}H_{30}N_2O_2.2HCl$=427.4
CAS — 32665-36-4 (eprozinol).
ATC — R03DX02.
ATC Vet — QR03DX02.
UNII — X9AMI360PL

Profile

Eprozinol hydrochloride has been given orally for its mucolytic or expectorant properties.

Adverse effects. Convulsions and coma were reported in a 19-year-old patient after taking eprozinol.[1]

1. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués de la pipérazine: (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; 32: 504–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Eupneron†.

Erdosteine *(BAN, rINN)*

Erdosteiini; Erdostein; Erdosteína; Erdostéine; Erdosteinum; Эрдостеин.
(±)-({[(Tetrahydro-2-oxo-3-thienyl)carbamoyl]methyl}thio) acetic acid.
$C_8H_{11}NO_4S_2$=249.3
CAS — 84611-23-4.
ATC — R05CB15.
ATC Vet — QR05CB15.
UNII — 76J0853EKA.

Uses and Administration

Erdosteine is a mucolytic that is used in the treatment of disorders of the respiratory tract characterised by productive cough (p. 1651.2). It is given in usual oral doses of 300 mg twice daily for a maximum of 10 days.

Doses may have to be reduced in hepatic impairment (see below).

Administration in hepatic and renal impairment. Exposure to erdosteine is increased in patients with hepatic impairment. UK licensed product information states that no increase in adverse effects has been seen in patients with mild hepatic impairment, but restricts the oral dose in these patients to a maximum of 300 mg daily. Erdosteine is contra-indicated in severe hepatic impairment as there is no experience of use in this group of patients.

Although no difference in absorption or elimination has been seen in patients with moderate renal impairment, the risk of accumulation of metabolites cannot be excluded. For this reason, use of erdosteine is contra-indicated in patients with a creatinine clearance of less than 25 mL/minute.

Chronic obstructive pulmonary disease. Erdosteine has been used[1-3] in the management of chronic obstructive pulmonary disease (p. 1199.1) but the value of mucolytics in this disorder is controversial and a recent review[4] considered the few published studies of erdosteine to be outdated and of poor quality.

1. Dechant KL, Noble S. Erdosteine. *Drugs* 1996; 52: 875–81.
2. Marchioni CF, *et al.* Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study). *Int J Clin Pharmacol Ther* 1995; 33: 612–18.
3. Moretti M, *et al.* The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: the EQUALIFE Study. *Drugs Exp Clin Res* 2004; 30: 143–52.
4. Anonymous. Erdosteine for COPD exacerbations. *Drug Ther Bull* 2008; 46: 79–80.

Adverse Effects and Precautions

Gastrointestinal disturbances may occur with erdosteine. Headache, dyspnoea, taste alterations, urticaria, erythema, and dermatitis have been reported rarely. Erdosteine should not be used in patients with active peptic ulcer disease. For precautions when used in patients with hepatic or renal impairment, see under Uses and Administration, above.

Pharmacokinetics

Erdosteine is rapidly absorbed after oral use and peak plasma concentrations occur after about an hour; absorption is unaffected by food. Erdosteine undergoes first-pass metabolism to an active metabolite, *N*-thiodiglycolyl-homocysteine. Plasma protein binding is about 64.5%. The elimination half-life is about 1.46 hours for erdosteine, and about 1.62 hours for the metabolite. It is mainly excreted in the urine as metabolites; faecal elimination is negligible.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fluidasa; *Austria*: Erdomed; *Belg.*: Mucodox; *Braz.*: Flusten; *Chile*: Biopulmin; *China*: A Duo Ting (阿多停); He Tan (和坦); Lu Chang (羅暢); Tantong (坦通); *Cz.*: Erdomed; *Denm.*: Erdotin; *Fin.*: Erdopect; *Fr.*: Vectrine; *Gr.*: Theovix; Tusselin; *Hung.*: Erdomed; *India*: Erdomac; Erdozet; *Indon.*: Edotin; Mucotein; Recustein; Vectrine; *Irl.*: Erdotin; *Israel*: Erdotin; *Ital.*: Erdotin; *Mex.*: Dostein; Esteclin; *Philipp.*: Ectrin; Zertin; *Pol.*: Erdomed; *Port.*: Erdotin†; *Switz.*: Mucofor; *Turk.*: Erdostin; Evosten; *UK*: Erdotin.

Multi-ingredient Preparations. *Mex.*: Esteclin Bac†.

Eriodictyon

Hierba santa; Mountain Balm; Yerba Santa; Эриодиктион калифорнийский.
CAS — 8013-08-9.
UNII — 2Y7TIQ135H.

NOTE. The name Hierba Santa (Yerba Santa) has been applied to many plants including *Artemesia absinthium* (p. 2426.1).

Profile

Eriodictyon consists of the dried leaves of *Eriodictyon californicum* (Hydrophyllaceae). It has been used as an expectorant. It has also been used in the treatment of dry mouth and to mask the taste of bitter drugs.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Mouth Kote.

Multi-ingredient Preparations. *Ger.*: Saliva natura; *Ital.*: Broncosedina; Broncosedina; *Switz.*: Hydro Santa†; *UK*: Saliva Natura; *USA*: Feminease; *Venez.*: Yerba Santa.

Homoeopathic Preparations. *Canad.*: Breathe More; *Fr.*: Boripharm No 11†; Santaherba; *Ger.*: A-Bomin; Broncho-Injektopas; Bronchopas; Pulmo Bronchialcomplex; Rufebran broncho†; Santa Flora S.

Etafedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Etafedrina, hidrocloruro de; Étafédrine, Chlorhydrate d'; Etafedrini Hydrochloridum; Ethylephedrine Hydrochloride; Hidrocloruro de etafedrina; Этафедрина Гидрохлорид.
(-)-2-(Ethylmethylamino)-1-phenylpropan-1-ol hydrochloride.
$C_{12}H_{19}NO.HCl$=229.7
CAS — 7681-79-0 (etafedrine); 48141-64-6 ((-)-etafedrine); 5591-29-7 (etafedrine hydrochloride).
UNII — Y134VQ304Y.

Profile

Etafedrine hydrochloride is a sympathomimetic related to ephedrine (p. 1663.1). It is used for its bronchodilator effects in combination preparations for the relief of cough and associated respiratory-tract disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: EMS Expectorante; Revenil Dospan; Revenil Expectorante; Revenil; Xpe Expectorante; *Canad.*: Dalmacol; ratio-Calmydone; *Indon.*: Decolsin; *S.Afr.*: *Nethaprin Dospan†*; *Nethaprin Expectorant†*; *Thai.*: Brondil†.

Ethyl Cysteine Hydrochloride

Etilcisteína, hidrocloruro de; Этиловый Эфир Цистеина Гидрохлорида.
Ethyl L-2-amino-3-mercaptopropionate hydrochloride.
$C_5H_{11}NO_2S.HCl$=185.7
CAS — 3411-58-3 (ethyl cysteine); 868-59-7 (ethyl cysteine hydrochloride).

Pharmacopoeias. In *Jpn.*

Profile

Ethyl cysteine hydrochloride is a mucolytic that has been used in the treatment of disorders of the respiratory tract associated with productive cough.

Preparations

Proprietary Preparations (details are given in Volume B).

Single-ingredient Preparations. *Jpn*: Cystanin.

Ethyl Orthoformate

Éther de Kay; Ortoformiato de etilo; Ortoformiato de trietilo; Triethoxymethane; Trietoximetano; Этиловый Эфир Ортомуравьиной Кислоты.
Triethyl orthoformate.
$C_7H_{16}O_3$=148.2
CAS — 122-51-0.

Pharmacopoeias. In *Fr.*

Profile

Ethyl orthoformate is a cough suppressant. It is reported to be a respiratory antispasmodic and has been given orally or rectally.

Fedrilate *(rINN)*

Fédrilate; Fedrilato; Fedrilatum; UCB-3928; Федрилат.
1-Methyl-3-morpholinopropyl perhydro-4-phenylpyran-4-carboxylate.
$C_{20}H_{29}NO_4$=347.5
CAS — 23271-74-1.
ATC — R05DB14.
ATC Vet — QR05DB14.
UNII — NT86R8M7J5.

Profile

Fedrilate is a cough suppressant used orally for non-productive cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Gotas Binelli.

Fenoxazoline Hydrochloride *(rINNM)* ⊗

Fénoxazoline, Chlorhydrate de; Fenoxazolini Hydrochloridum; Hidrocloruro de fenoxazolina; Феноксазолина Гидрохлорид.
2-(2-Isopropylphenoxymethyl)-2-imidazoline hydrochloride.
$C_{13}H_{18}N_2O.HCl$=254.8
CAS — 4846-91-7 (fenoxazoline); 21370-21-8 (fenoxazoline hydrochloride).
ATC — R01AA12.
ATC Vet — QR01AA12.
UNII — 6K28Y09857.

Profile

Fenoxazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3) that has been used topically for its vasoconstrictor properties in the symptomatic treatment of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nebulicina; *Braz.*: Nasofelin; Rinigran.

Fominoben Hydrochloride *(rINNM)*

Fominobén, hidrocloruro de; Fominobène, Chlorhydrate de; Fominobeni Hydrochloridum; Hidrocloruro de fominobén; PB-89; Фоминобена Гидрохлорид.
3'-Chloro-2'-[*N*-methyl-*N*-(morpholinocarbonylmethyl)aminomethyl]benzanilide hydrochloride.
$C_{21}H_{24}ClN_3O_3.HCl$=438.3
CAS — 18053-31-1 (fominoben); 24600-36-0 (fominoben hydrochloride).
UNII — XCT2R4O51G.

Profile

Fominoben hydrochloride is a centrally acting cough suppressant that is also reported to have respiratory stimulant properties. It is used for cough (p. 1651.2) and is given in oral doses of 160 mg up to three times daily; it has also been given by slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Noleptan†; *Mex.*: Noleptan.

Fudosteine *(rINN)*

Fudosteina; Fudostéine; Fudosteinum; SS-320A; Фудостеин.
(-)-3-[(3-Hydroxypropyl)thio]-L-alanine.
$C_6H_{13}NO_3S$=179.2
CAS — 13189-98-5.
UNII — UR9VPI71PT.

Profile

Fudosteine is an expectorant given orally in a dose of 400 mg three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Zhong Chang (中畅); *Jpn*: Cleanal; Spelear.

Glaucine

Boldine Dimethyl Ether; DL-832 (*dl*-glaucine phosphate); *dl*-Glaucine; Glaucina; MDL-832 (*dl*-glaucine phosphate); Глауцин.
DL-1,2,9,10-Tetramethoxyaporphine.
$C_{21}H_{25}NO_4$=355.4
CAS — 5630-11-5 (dl-glaucine); 73239-87-9 (dl-glaucine phosphate); 475-81-0 (d-glaucine); 5996-06-5 (d-glaucine hydrobromide).
UNII — NU19306XA7.

Profile

Glaucine is a centrally acting cough suppressant used in non-productive cough; it has been given as the phosphate.

d-Glaucine has also been used, as the hydrobromide and the hydrochloride. It has been obtained from *Glaucium flavum* (Papaveraceae).

Abuse. A 23-year-old woman developed nausea and vomiting within 30 minutes of taking 2 tablets described as "head candy" or as a BZP-free "herbal high".[1] This was followed by a period of dissociative-type symptoms and later by agitation, tachycardia, and tachypnoea. Analysis of serum and urine revealed the presence of glaucine.

1. Dargan PI, *et al.* Detection of the pharmaceutical agent glaucine as a recreational drug. *Eur J Clin Pharmacol* 2008; 64: 553–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Glauvent (Глаувент).

Multi-ingredient Preparations. *Rus.*: Bronchitussin (Бронхитуссев); Bronchocin (Бронхоцин); Broncholytin (Бронхолитин); Bronchoton (Бронхотон); *Ukr.*: Broncholytin (Бронхолитин).

Guacetisal *(rINN)*

Acetylsalicylic Acid Guaiacol Ester; Guacétisal; Guacetisalum; Гуацетисал.
o-Methoxyphenyl salicylate acetate.
$C_{16}H_{14}O_5$=286.3
CAS — 55482-89-8.
ATC — N02BA14.
ATC Vet — QN02BA14.
UNII — T6EKB9V2O2.

Profile

Guacetisal has been used in respiratory disorders as an expectorant. It has also been used as an antipyretic to reduce fever. It has been given orally and rectally.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Suo Di Fei (索迪菲).

Guaiacol

Gaiacol; Guaiacolum; Guajacol; Guayacol; Gwajakol; Methyl Catechol; Гваякол.
2-Methoxyphenol.
$C_7H_8O_2$=124.1.
CAS — 90-05-1 (guaiacol); 553-17-3 (guaiacol carbonate); 60296-02-8 (calcium guaiacolglycolate); 4112-89-4 (guaiacol phenylacetate).
UNII — 6JKA7MAH9C.

Pharmacopoeias. In *Eur.* (see p. vii). *Fr.* also includes guaiacol carbonate.

Ph. Eur. 8: (Guaiacol). A crystalline mass or colourless or yellowish hygroscopic liquid. Sparingly soluble in water; freely soluble in alcohol; very soluble in dichloromethane. Store in airtight containers. Protect from light.

Profile

Guaiacol has disinfectant properties and has been used in dentistry and as an expectorant for productive cough.

In high concentrations, adverse effects are similar to, but less severe than, those of phenol (p. 1764.2).

Many salts and derivatives of guaiacol have been used similarly including the carbonate, cinnamate, ethylglycolate, calcium and sodium glycolates, phenylacetate, and phenylbutyrate. See also Guaifenesin, below and Sulfoguaiacol, p. 1678.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Eucaliptine†.

Multi-ingredient Preparations. *Arg.*: Aseptobron; Atomo Desinflamante Familiar; Atomo Desinflamante; *Belg.*: Eucalyptine Pholcodine; Inopectol†; *Braz.*: Ozonyl; Transpulmin Balsamo; Transpulmin; *Canad.*: Creo-Rectal; Demo-Cineol†; *Fr.*: Aldyzine; Bi-Qui-Nol; Bronchorectine au Citral; Essence Algerienne; Osomol; Pastiserol†; Pulmo Bailly; Pulmoserum; Rockles; Valda†; *India*: Mynberrys Compound; *Ital.*: Eugenol-Guaiacolo Composto; Fosfoguaiacol†; Lipobalsamo; *Mex.*: Guayalin; *Mon.*: Bronchodermine; Bronchodermine; *Port.*: Algina; *Spain*: Bronco Aseptilex Fuerte†; Tos Mai; *UK*: Dragon Balm; Pulmo Bailly; *USA*: Methagual.

Homoeopathic Preparations. *Canad.*: Hylagesic APF.

Guaietolin *(rINN)*

Glyceylguethol; Glyguetol; Guaietolina; Guaiétoline; Guaietolinum; Guayetolina; Гвайэтолин.
3-(2-Ethoxyphenoxy)propane-1,2-diol.
$C_{11}H_{16}O_4$=212.2
CAS — 63834-83-3.
UNII — G9J54386JH.

Profile

Guaietolin is an analogue of guaifenesin (below) which is used as an expectorant. It has been given for cough (p. 1651.2) in oral doses of 300 to 600 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Guethural.

Guaifenesin *(BAN, USAN, rINN)*

Glicerilguayacol; Glyceryl Guaiacolate; Glyceylguayacolum; Guaiacol Glycerol Ether; Guaiacyl Glyceryl Ether; Guaifenesiini; Guaifenesina; Guaifénésine; Guaifénésine; Guaifenesinum; Guaiphenesin; Guajacolum Glycerolatum; Gvajfenezin; Gvajfenezinas; Гвайфенезин.
(*RS*)-3-(2-Methoxyphenoxy)propane-1,2-diol.
$C_{10}H_{14}O_4$=198.2
CAS — 93-14-1.
ATC — R05CA03.
ATC Vet — QM03BX90; QR05CA03.
UNII — 495W7451VQ.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Guaifenesin). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol.

USP 36: (Guaifenesin). A white to slightly grey crystalline powder. May have a slight characteristic odour. Soluble 1 in 60 to 70 of water; soluble in alcohol, in chloroform, and in propylene glycol; sparingly soluble in glycerol. Store in airtight containers.

Uses and Administration

Guaifenesin is reported to increase the volume and reduce the viscosity of tenacious sputum and is used as an expectorant for productive cough (see Respiratory Disorders, below). It is given in oral doses of 200 to 400 mg every 4 hours. In the USA, a maximum of 6 doses daily is allowed; however, in the UK, it is more usual to giv 4 times daily. Modified-release preparations, given every 1 hours, are also available. For doses in children, see below.

Guaifenesin has been used similarly as the calcium salt

Guaifenesin is used as an adjunct to anaesthesia i veterinary medicine.

Administration in children. Guaifenesin is licensed for us as an expectorant in children. However, over-the-counte cough and cold preparations containing expectorant (including guaifenesin) should be used with caution i children and generally avoided in young children; fo details, see Cough, p. 1651.2.

In the USA, typical licensed oral doses, given every hours, according to age, are:

- 4 to 6 years, 50 to 100 mg
- 6 to 12 years, 100 to 200 mg

Modified-release preparations, given every 12 hours, ar also available.

In the UK, licensed product information suggests tha these doses may be given up to a maximum of 4 times daily

Respiratory disorders. An FDA review of preparation available over-the-counter concluded that guaifenesin wa an effective expectorant.[1] The use of expectorants for pro ductive cough is discussed on p. 1651.2. A small study found that guaifenesin also appeared to reduce coug reflex sensitivity in patients with upper respiratory-trac infections, which produce a transient increase in sensitiv ity, although it had no effect on cough reflex in healthy subjects. The mechanism for this effect was unclear.

1. Thomas J. Guaiphenesin—an old drug now found to be effective. *Aust Pharm* 1990; 71: 101–3.
2. Dicpinigaitis PV, Gayle YE. Effect of guaifenesin on cough reflex sensitivity. *Chest* 2003; 124: 2178–81.

Adverse Effects and Precautions

Gastrointestinal discomfort, nausea, and vomiting have occasionally been reported with guaifenesin, particularly ir very large doses.

Abuse. Urinary calculi have been reported in patients consuming large quantities of over-the-counter preparations containing guaifenesin.[1,2] Spectroscopic analysis[1] revealed that the stones were composed of a calcium salt of beta-(2-methoxyphenoxy)-lactic acid, which is a metabolite of guaifenesin. Small quantities of ephedrine were also present in the stones of one of several patients who had ingested preparations containing a combination of guaifenesin and ephedrine.[2]

1. Pickens CL, *et al.* Abuse of guaifenesin-containing medications generates an excess of a carboxylate salt of beta-(2-methoxyphenoxy)-lactic acid, a guaifenesin metabolite, and results in urolithiasis. *Urology* 1999; 54: 23–7.
2. Assimos DG, *et al.* Guaifenesin- and ephedrine-induced stones. *J Endourol* 1999; 13: 665–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies guaifenesin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pharmacokinetics

Guaifenesin is well absorbed from the gastrointestinal tract. It is metabolised and then excreted in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Guaifen; Omega 100 Bronquial; Plenum; Vick 44 Exp; Vickmiel; *Austral.*: Actifed CC Chesty†; Robitussin Chesty Cough; Robitussin EX†; Vicks Cough Syrup for Chesty Cough; Vicks Formula 44 Chesty Cough†; *Austria*: Resyl; *Belg.*: Vicks Vaposyrup Expectorant; *Braz.*: Broncofenil; Dimetapp Expectorante†; Expectovic; Transpulmin; Vick Xarope; Xarope Vick Mel; *Canad.*: Balminil Expectorant; Benylin Chest Congestion; Benylin DM-D-E-A Cold and Sinus; Benylin E†; Bronchophan Expectorant; Cold and Flu-in-One; Cough Syrup Expectorant; Expectorant Cough Formula; Expectorant Syrup; Expectorant; Robitussin; Vicks Chest Congestion Relief; Vicks DayQuil Mucus Control; *Cz.*: Coldrex Broncho; Guajacuran; Robitussin Expectorans; *Fin.*: Tinrus; *Fr.*: Vicks Expectorant; *Ger.*: Fagusan; Wick Husten-Loser; *Gr.*: VP-Syrup; *Hong Kong*: Breacol; G.G. Tab†; Glylate; Gufensin; Mucolex†; Neotussin†; Robitussin Chest Congestion†; Robitussin EX; Uni-Colex; *Hung.*: Coldrex Broncho†; Relaxil-G; Robitussin Expectorans; *India*: Barkeit; *Indon.*: Probat; *Irl.*: Benylin Childrens Chesty Cough; Lemsip Chesty Cough; Meltus Honey and Lemon†; Robitussin Chesty Cough; Tixylix Chesty Cough; *Israel*: Kuffex DM; Resyl; Robitussin; Vitussin; *Ital.*: Broncovanil; Resyl; Vicks Tosse Fluidificante; *Malaysia*: Guafensin; Mucinex; *Mex.*: Robitussin; Tukol†; Vick 44 Exp; *Norw.*: Tussin; *NZ*: Mucinex; Robitussin EX; *Philipp.*:

Bena; Benadryl Expectorant; Flemonex; Guais†; Pharmachem; Robitussin Expectorant; Suprekof; Transpulmin G; Venalax XPT: *Pol.*: Guajavis; Guajazyl; Robitussin Expectorans; *Port.*: Vicks Xarope Expectorante; *Rus.*: Coldrex Broncho (Колдрекс Бронхо); Novo-Passit (Ново-Пассит); Theraflu KV (Терафлю КВ); Tussin (Тусин); *S.Afr.*: Actospect; Benylin Wet Cough; Borstol Linctus†; Broncholin; Chamberlains Cough Remedy Honey and Liquorice†; Chamberlains Cough Remedy Peppermint†; Dilinct Junior; Expelinct; Flemmi-Ped†; Med-Lemon Cough Syrup†; Vicks Acta Plus Expectorant†; *Singapore*: Breacol; Cofen; Decosyn; Guardian Cough; Robitussin EX; Wood's Peppermint Cough Syrup; *Spain*: Formulaexpec; Frispec; *Swed.*: Resyl†; Theracough; *Switz.*: Resyl; Vicks Sirop Expectorant; *Thai.*: Fenesin; Genesin; Glycolate; Glyryl; Guaiacol; Kidkof; Mulade; Robitussin; Tussa†; *Turk.*: Vicks Vapo Expectorant; Vicks VapoSyrup; *UK*: Adult Chesty Cough Non Drowsy; Benylin Childrens Chesty Coughs; Benylin Mucus Cough Honey & Lemon; Benylin Mucus Cough Menthol; Boots Chesty Cough Syrup 6 Years Plus; CalCough Six Plus; Expectorant Cough Syrup; Hill's Balsam Chesty Cough; Jackson's All Fours; Jackson's Bronchial Balsam; Lemsip Cough & Cold Chesty Cough; Robitussin Chesty Cough; Tixylix Chesty Cough; Venos for Kids; Vicks Cough Syrup for Chesty Coughs; Vicks Vaposyrup for Chesty Coughs; *USA*: Bidex; Buckleys Chest Congestion; Diabetic Tussin Mucus Relief; Ganidin NR†; Glycotuss; Guiatuss; Humavent; Humibid Maximum Strength; Iophen NR; Liquibid; Liquituss GG; Mucinex; MucusRelief; Naldecon Senior EX; Organ-I NR; Organidin NR; Refenesen; Robitussin Mucus & Chest Congestion; Scot-Tussin Expectorant; Siltussin; Tusibron; Vicks Dayquil Mucus Control; Xpect; *Venez.*: Alivetos Pediatrico; Robitessin.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Dyphylline and Guaifenesin Elixir; Dyphylline and Guaifenesin Tablets; Guaifenesin and Codeine Phosphate Syrup; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin Capsules; Guaifenesin Syrup; Guaifenesin Tablets; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Theophylline and Guaifenesin Capsules; Theophylline and Guaifenesin Oral Solution.

Guaimesal *(rINN)*

Guaimésal; Guaimesalum; Гваймесал.

(±)-2-(*o*-Methoxyphenoxy)-2-methyl-1,3-benzodioxan-4-one.

$C_{16}H_{14}O_5$=286.3

CAS — 81674-79-5.

UNII — K43273G1CW.

Profile

Guaimesal is reported to have expectorant and antipyretic properties and has been given orally as an adjunct in the treatment of respiratory-tract disorders. It has also been given rectally in suppositories.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pak.*: Brontermil.

Helicidine

Helicidina; Helixinum; Гелицидин.

Profile

Helicidine is a mucoglycoprotein from the snail *Helix pomatia* that has been used as a cough suppressant.

References.

1. Pons F, *et al.* L'effect bronchorelaxant de l'helicidine, un extrait d'Helix pomatia, fait intervenir une liberation de prostaglandine E2. *Pathol Biol (Paris)* 1999; 47: 73–80.

Indanazoline Hydrochloride *(rINNM)* ⊗

Hidrocloruro de indanazolina; Indanazolin Hidroklorür; Indanazolina, hidrocloruro de; Indanazoline, Chlorhydrate d'; Indanazolini Hydrochloridum; Инданазолина гидрохлорид.

$C_{12}H_{15}N_3$,HCl=237.7.

CAS — 56601-85-5.

UNII — 2364A90IV8.

Profile

Indanazoline is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It has been used as the hydrochloride for its vasoconstrictor effect in the management of nasal congestion (p. 1652.1). It has been given as nasal drops, a nasal gel, or a nasal spray in a concentration equivalent to indanazoline 0.1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Farial.

Iodinated Glycerol *(BAN, USAN)*

Glicerol yodado; Iodopropylidene Glycerol; Глицерин йодированный.

$C_6H_{11}IO_3$=258.1

CAS — 5634-39-9.

UNII — 34ON63CC03.

Profile

Iodinated glycerol, a methyl derivative of domiodol, is an isomeric mixture of iodinated dimers of glycerol. It has been used as an expectorant. The limitations of iodides as expectorants are discussed in Cough on p. 1651.2. The actions of iodides and iodine compounds are discussed under Iodine p. 2336.3. Prolonged use of iodinated glycerol has been associated with thyroid dysfunction (see Effects on the Thyroid Gland, below) and severe skin eruptions; gastrointestinal disturbances and hypersensitivity reactions have also occurred. Malignant neoplasms have developed in *animals* given iodinated glycerol.

Chronic obstructive pulmonary disease. Studies[1-3] of the use of iodinated glycerol in patients with chronic bronchitis have produced conflicting results. The use of mucolytics or expectorants in chronic obstructive pulmonary disease (p. 1199.1) is controversial.

1. Petty TL. The National Mucolytic Study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990; 97: 75–83.
2. Repsher LH. Treatment of stable chronic bronchitis with iodinated glycerol: a double-blind, placebo-controlled trial. *J Clin Pharmacol* 1993; 33: 856–60.
3. Rubin BK, *et al.* Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996; 109: 348–52.

Effects on the thyroid gland. Thyroid dysfunction (both hyperthyroidism and hypothyroidism) has developed after giving iodinated glycerol to previously euthyroid patients. It was recommended that baseline thyroid function tests should be carried out before starting treatment with iodinated glycerol;[1] it should be withdrawn if abnormal results are obtained during use.

1. Gittoes NJL, Franklyn JA. Drug-induced thyroid disorders. *Drug Safety* 1995; 13: 46–55.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Iophen; Par Glycerol; R-Gen.

Ipecacuanha

Hlavěnkový kořen; Ipecac; Ipecacuana; Ipécacuanha, racine d'; Ipecacuanha Root; Ipecacuanhae Radix; Ipecacuanhawurzel; Ipekakuanų šaknys; Ipekakuána-gyökér; Ipekakuananjüüri (ipecacuanha root); Ipekakuanarot (ipecacuanha root); Korzeń ipekakuany; Raiz de ipecacuana; Ипекакуана.

CAS — 8012-96-2.

ATC — R05CA04; V03AB01.

ATC Vet — QR05CA04; QV03AB01.

ATC Herb — HV03AB5002 (Psychotria ipecacuanha: root); HP01AW5001 (Cephaelis acuminata: root); HR05WA5048 (Psychotria ipecacuanha: root); HR05WA5002 (Cephaelis acuminata: root); HP01AW5002 (Psychotria ipecacuanha: root); HV03AB5001 (Cephaelis acuminata: root).

UNII — 62I3C8Z33L

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Eur., *Jpn*, and *US* also include a monograph for Prepared Ipecacuanha or a similar standardised form.

Ph. Eur. 8: (Ipecacuanha Root; Ipecacuanha BP 2014). It consists of the fragmented and dried underground organs of *Cephaelis ipecacuanha* known as Matto Grosso ipecacuanha, or of *C. acuminata* known as Costa Rica ipecacuanha, or a mixture of both species. It contains not less than 2.0% of total alkaloids, calculated as emetine. It has a slight odour. Store in airtight containers. Protect from light.

The BP 2014 directs that when Ipecacuanha, Ipecacuanha Root, or Powdered Ipecacuanha is prescribed or demanded, Prepared Ipecacuanha shall be dispensed or supplied.

Ph. Eur. 8: (Ipecacuanha, Prepared; Ipecacuanhae Pulvis Normatus). It is ipecacuanha root powder adjusted to an alkaloidal content of 1.9 to 2.1% of total alkaloids, calculated as emetine. Store in airtight containers. Protect from light.

USP 36: (Ipecac). The dried rhizome and roots of *Cephaelis acuminata* or of *C. ipecacuanha* (Rubiaceae). It yields not less than 2% of ether-soluble alkaloids of which not less than 90% is emetine and cephaeline; the content of cephaeline varies from an amount equal to, to an amount not more than 2.5 times, that of emetine.

USP 36: (Powdered Ipecac). It contains 1.9 to 2.1% of ether-soluble alkaloids, with emetine and cephaeline content as for Ipecacuanha. It is pale brown, weak yellow, or light olive-grey powder that should be stored in airtight containers.

Uses and Administration

Ipecacuanha has been used as an **expectorant** in productive cough (p. 1651.2) in doses of up to about 1.4 mg of total alkaloids. Compound preparations of ipecacuanha, such as Desessartz syrup, have also been used in respiratory disorders.

Ipecacuanha may also be used in larger doses as an **emetic** but is of very limited value (see Poisoning, below). Vomiting usually occurs within 30 minutes of an oral emetic dose, due to an irritant effect on the gastrointestinal tract and a central action on the chemoreceptor trigger zone. Doses are usually followed by a copious drink of water or fruit juice. Adults have been given doses of about 42 mg of total alkaloids; each 5 mL of Ipecac Syrup (USP 36) supplies about 7 mg of total alkaloids. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred. For doses in children, see below.

Homoeopathy

Ipecacuanha has been used in homoeopathic medicines under the following names: Ipeca; Cephaelis ipecacuanha; Ipecac.

Administration in children. Over-the-counter cough and cold preparations containing expectorants (including ipecacuanha) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

In the UK, induction of emesis with ipecacuanha is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration (but see also Poisoning, below).

In the USA, children aged 6 months to 1 year have been given about 7 to 14 mg of total alkaloids and older children about 21 mg. Each 5 mL of Ipecac Oral Solution (USP 36) supplies about 7 mg of total alkaloids. Doses are usually followed by a copious drink of water or fruit juice; in young children this may be given before the dose. Doses may be repeated once only after 20 to 30 minutes if emesis has not occurred.

Poisoning. Measures to reduce absorption of the toxic substance, such as stomach emptying, have often been advocated in the management of acute poisoning (p. 1537.1). Ipecacuanha has been used to induce emesis, but is no longer routinely recommended. It may be considered in alert, conscious patients, if a potentially life-threatening amount of toxic substance has been ingested within the preceding hour, and where other measures are unavailable or inappropriate.

Adverse Effects

Large doses of ipecacuanha have an irritant effect on the gastrointestinal tract, and persistent bloody vomiting or bloody diarrhoea may occur. Mucosal erosions of the entire gastrointestinal tract have been reported. The absorption of emetine, which is most likely if vomiting does not occur after emetic doses of ipecacuanha, may give rise to adverse effects on the heart, such as conduction abnormalities or myocardial infarction. These, combined with dehydration due to vomiting may cause vasomotor collapse followed by death.

There have been several reports of chronic abuse of ipecacuanha to induce vomiting in eating disorders; cardiotoxicity and myopathy have occurred and may be a result of accumulation of emetine.

There have also been several reports of ipecacuanha poisoning due to the unwitting substitution of Ipecac Fluidextract (a former USP preparation) for Ipecac Syrup (USP); the fluidextract was about 14 times the strength of the syrup.

References.

1. Manno BR, Manno JE. Toxicology of ipecac: a review. *Clin Toxicol* 1977; 10: 221–42.

Hypersensitivity. Allergy, characterised by rhinitis, conjunctivitis, and chest tightness, has occurred due to inhalation of ipecacuanha dust in packers of ipecacuanha tablets.[1]

1. Luczynska CM, *et al.* Occupational allergy due to inhalation of ipecacuanha dust. *Clin Allergy* 1984; 14: 169–75.

Vomiting. Prolonged vomiting has been reported in 17% of patients given ipecacuanha in the treatment of poisoning and may lead to gastric rupture, Mallory-Weiss tears of the oesophagogastric junction, cerebrovascular events, and pneumomediastinum and pneumoperitoneum.[1]

1. Bateman DN. Adverse reactions to antidotes. *Adverse Drug React Bull* 1988; 133: (Dec.): 496–9.

Treatment of Adverse Effects

After acute overdose of ipecacuanha, activated charcoal is given to delay absorption followed if necessary by gastric lavage. Prolonged vomiting may be controlled by the injection of antiemetics. Fluid and electrolyte imbalance should be corrected and facilities should be available to correct any cardiac effects and subsequent shock.

When ipecacuanha is withdrawn after chronic abuse, recovery may be prolonged due to the slow elimination of emetine.

Precautions

The use of emetics is now rarely favoured; in particular, ipecacuanha should not be used as an emetic in patients who are unconscious or whose condition otherwise increases the risk of aspiration, nor in patients who have taken substances, such as corrosive compounds or petroleum products, that might be especially dangerous if aspirated. Ipecacuanha should not be given to patients in shock or to those at risk from seizures either as a result of their condition or from compounds, such as strychnine, that have been ingested. Patients with cardiovascular disorders are at risk if ipecacuanha is absorbed.

Abuse. Ipecac syrup has been abused by patients with eating disorders to induce vomiting.[1] Adverse effects of repeated vomiting, such as metabolic complications, aspiration pneumonitis, parotid enlargement, dental abnormalities, and oesophagitis or haematemesis due to mucosal lacerations (the Mallory-Weiss syndrome) may be seen. Cardiotoxicity may occur and fatalities have been reported including one patient who had ingested 90 to 120 mL of ipecac syrup daily for 3 months.[2] It has been suggested that cardiac effects and myopathy after the prolonged abuse of ipecac syrup may be due to the long-term accumulation of emetine[3,4] but some have expressed doubts.[5]

Cardiomyopathy has also been reported in children given ipecacuanha to produce factitious illness (Munchausen's syndrome by proxy);[6-8] fatalities have occurred.

1. Harris RT. Bulimarexia and related serious eating disorders with medical complications. *Ann Intern Med* 1983; 99: 800–7.
2. Adler AG, *et al.* Death resulting from ipecac syrup poisoning. *JAMA* 1980; 243: 1927–8.
3. Palmer EP, Guzy AT. Reversible myopathy secondary to abuse of ipecac in patients with major eating disorders. *N Engl J Med* 1985; 313: 1457–9.
4. Pope HG, *et al.* The epidemiology of ipecac abuse. *N Engl J Med* 1986; 314: 243–6.
5. Isner JM. Effects of ipecac on the heart. *N Engl J Med* 1986; 314: 1253.
6. Goebel J, *et al.* Cardiomyopathy from ipecac administration in Munchausen syndrome by proxy. *Pediatrics* 1993; 92: 601–3.
7. Schneider DJ, *et al.* Clinical and pathologic aspects of cardiomyopathy from ipecac administration in Munchausen's syndrome by proxy. *Pediatrics* 1996; 97: 902–6.
8. Carter KE, *et al.* Munchausen syndrome by proxy caused by ipecac poisoning. *Pediatr Emerg Care* 2006; 22: 655–6.

Interactions

The action of ipecacuanha may be delayed or diminished if it is given with or after charcoal; antiemetics may also reduce its effect.

Food. *Milk* had been believed to impair the emetic efficacy of ipecacuanha but there was no significant difference in the time to onset of vomiting, the duration of vomiting, or the number of episodes in 250 children who were given ipecac syrup with milk compared with 250 given ipecac syrup with clear fluids.[1]

1. Klein-Schwartz W, *et al.* The effect of milk on ipecac-induced emesis. *J Toxicol Clin Toxicol* 1991; 29: 505–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Ipecavom: *UK*: Fennings Little Healers.

Multi-ingredient Preparations. *Arg.*: No-Tos Infantil; No-Tos Infantil; *Braz.*: Expec; Expectomel; Fenergan Expectorante; Iodesin; KI-Expectorante; Melagriao; Pilulas Ross; *Chile*: Pectokast; *Fr.*: Phytotux; *Ger.*: Weleda Hustenelixier; *Gr.*: Neo-Bronchoton-R; Torylet; *Hong Kong*: Pritussin†; Uni-Cophedene†; *Indon.*: Andonex; Koffex for Children; Prome; Promedex; Promethazine Ikapharmindo; *Irl.*: Venos Honey & Lemon; *Israel*: Doveri†; Laxative Compound; Promethazine Expectorants; Prothiazine Expectorant; *Neth.*: Promethazine comp†; *Port.*: Stodal; *Rus.*: Prothiazine Expectorant (Пропазин Экспекторант); *S.Afr.*: Chamberlains Cough Remedy Regular†; Cough Elixir†; Linctus Tussi Infans†; SB Cirogin Cough Mixture†; *Singapore*: Beacons Cough; Pico's Children's Cough; PO-V-SU; Robinson Cough; Sunny Children Cough; Veelanz's Cough Syrup; Williams Cough; *Spain*: Alofedina; Buco Regis; Fenergan Expectorante; *Switz.*: Bromocod N†; Demo Elixir pectoral N†; DemoPectol; Elixir contre la toux†; Neo-Codion N; Pastilles pectorales du Dr. Welti; *UK*: Allens Dry Tickly Cough; Allens Pine & Honey; Asthma & Catarrh Relief; Beehive Balsam; Buttercup Infant Cough Syrup; Buttercup Syrup (Blackcurrant flavour); Buttercup Syrup (Honey and Lemon flavour); Cough-eeze; Covonia Herbal Mucus Cough Syrup; Galloway's Cough Syrup; Hill's Balsam Chesty Cough for Children; Hill's Balsam Chesty Cough Pastilles; Hill's Balsam Extra Strong; Honey & Molasses; Jackson's Troublesome Coughs; Kilkof; Lockets Medicated Linctus; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Vegetable Cough Remover; *USA*: Poison Antidote Kit; Quelidrine; *Venez.*: Codebromil; Dromil Sauco; Novacodin; Tabonuco; Tessamag con Codeina.

Homoeopathic Preparations. *Austral.*: Childrens Cough Relief; Respatona Chesty Cough & Nasal Congestion; *Austria*: Nausyn; Nisylen†; Pertudoron†; Pulsatilla Med Complex; Tonsan chronisch; toxi-loges; *Canad.*: Breathe More; Brocosin; Bronkeel†; Cough & Cold; Cough Syrup with Honey†; Diarrhea; Drosera Complex; Drosera Plex†; Homeo-Form G†; Homeo-Form R†; Hyalgesic HP†; Hylands Formula CS; Hylands Headache; Jet Lag; Pertudoron 1†; Phytotux H; Stodal; *Chile*: Pertussin; Similibus; Cz.: Bronchalis-Heel; Drosetux; Stodal; *Fr.*: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 67†; Abbe Chaupitre no 91†; Baudry; Boripharm No 15†; Cetraria Complexe No 61; Drosera Complexe No 64; Drosera Compose; Hepatocynesine†; Homeogene 14†; Homeogrippe†; Ipeca Complexe No 65; Ipeca Compose; L 107; Nux Vomica Complexe No 49; Pates Pectorales; Pertudoron; Poconeol no 48; Pulmo-Drainol†; Santaherba; Stodal; Stodal; Tabacum Compose; *Ger.*: Bronchiselect; Broncho-Injektopas; Bronchopas; Gastro Magentabletten; Monapax; Mucosa compositum; Nisylen; Pertudoron 1; Procordal vertigo; toxi-loges; toxi-loges; Tussiflorin Hom; Tussisana; Tussistin S; Tussistin; Viropect; *Hung.*: Stodal; *Neth.*: Bronchalis; Drosinula; Gravifem†; Homeocare siroop; Kind 0-6 Nisykind; Kind 0-6 Tussikind; Kind 0-6 Tussikind; Mucosa comp H; Nectadyn H; Nisyleen; Stodal; Travelin; Tussistin; *Rus.*: Influcid (Инфлюцид); Stodal (Стодаль); *S.Afr.*: Pertudoron Drops†; *Switz.*: Drosetux; Regenaplex Nr 38b; TussEx; *UK*: Cough Elixir; Nausyn; *Ukr.*: Influcid (Инфлюцид); Stodal (Стодаль).

Pharmacopoeial Preparations
BP 2014: Paediatric Ipecacuanha Emetic Mixture;
Ph. Eur.: Ipecacuanha Liquid Extract, Standardised; Ipecacuanha Tincture, Standardised;
USP 36: Ipecac Oral Solution.

Isoaminile *(BAN, rINN)*

Isoaminiili; Isoaminil; Isoaminilo; Isoaminilum; Изоаминил.
4-Dimethylamino-2-isopropyl-2-phenylpentanonitrile.
$C_{16}H_{24}N_2$=244.4
CAS — 77-51-0.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — R4823W2PQL.

Isoaminile Citrate *(BANM, rINNM)*

Citrato de isoaminilo; Isoaminile, Citrate d'; Isoaminili Citras; Isoaminilo, citrato de; Изоаминила Цитрат.
4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile dihydrogen citrate.
$C_{16}H_{24}N_2C_6H_8O_7$=436.5
CAS — 126-10-3; 28416-66-2.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — 27K34XSD46.

Isoaminile Cyclamate *(rINNM)*

Ciclamato de isoaminilo; Isoaminile, Cyclamate d'; Isoaminili Cyclamas; Изоаминила Цикламат.
4-Dimethylamino-2-isopropyl-2-phenylvaleronitrile cyclohexanesulfamate.
$C_{16}H_{24}N_2C_6H_{13}NO_3S$=423.6
CAS — 10075-36-2.
ATC — R05DB04.
ATC Vet — QR05DB04.
UNII — 4055851484.

Profile

Isoaminile is a centrally acting cough suppressant that has been given orally; the citrate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Peracon: *Indon.*: Peracon; *Turk.*: Peracon.

Levmetamfetamine *(USAN, rINN)* ⊗

l-Deoxyephedrine; L-Desoxiefedrina; L-Desoxyephedrine; Lesoxyephedrine; Levmétamfétamine; Levmetamfetaminum; Levmetanfetamina; Levometanfetamina; *l*-Methamphetamine; *l*-Methylamphetamine; Левметамфетамин.
(*R*)-*N*,α-Dimethylbenzeneethanamine; (-)-(*R*)-*N*,α-Dimethylphenethylamine.
$C_{10}H_{15}N$=149.2
CAS — 33817-09-3.
UNII — Y24T98T2Q2.

Pharmacopoeias. In *US.*

USP 36: (Levmetamfetamine). A clear, practically colorless, liquid. Store in airtight containers. Protect from light.

Profile

Levmetamfetamine is the *laevo* isomer of metamfetamine (p. 2324.2) and is used topically in the treatment of nasal congestion.

References.
1. Mendelson JE, *et al.* The clinical pharmacology of intranasal l-methamphetamine. *BMC Clin Pharmacol* 2008; 8: 4. Available at: http://www.biomedcentral.com/content/pdf/1472-6904-8-4.pdf (accessed 02/07/09)

Abuse. Levmetamfetamine is a less potent central stimulant than metamfetamine, but it has been subject to occasional abuse.[1,2] In addition, as a stimulant, its use is prohibited in sport during competition.[3]

1. Halle AB, *et al.* Drug abuse with Vicks nasal inhaler. *South Med J* 1955; 78: 761–2.
2. Ferrando RL, *et al.* Bizarre behavior following the ingestion of levodesoxyephedrine. *Drug Intell Clin Pharm* 1988; 22: 214–17.
3. World Anti-Doping Agency. The world anti-doping code: the 2010 prohibited list international standard. Available at: http://www.wada-ama.org/Documents/World_Anti-Doping_Program/WADP-Prohibited-list/WADA_Prohibited_List_2010_EN.pdf (accessed 01/12/09)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Vicks Vapor Inhaler.

Marrubium

Andornkraut; Herba Marrubii; Hurtanminttu; Jablečníková nať; Juanrubio; Kransborre; Malva de sapo; Malvarrubio; Marrube blanc, parties aériennes fleuries de; Marrubii herba; Marrubio; Šantrų žolė; White Horehound; Шандра Обыкновенная.
ATC Herb — HA09WA5016 (Marrubium vulgare: *herb*); *HR05WA5028* (Marrubium vulgare: *herb*); *HA05AW5012* (Marrubium vulgare: *herb*).
UNII — 7A72MUN24Z (Marrubium vulgare *whole*); *K08036XEJV* (Marrubium vulgare *leaf*).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (White Horehound). The whole or fragmented dried flowering aerial parts of *Marrubium vulgare*. It contains a minimum 0.7% of marrubiin ($C_{20}H_{28}O_4$=332.4), calculated as the dried drug.

Profile

Marrubium is the flower or leaf of *Marrubium vulgare* (Labiatae). It has been used for its supposed expectorant properties in herbal preparations for the treatment of coughs. It has also been used as a flavouring.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Angocin Bronchialtropfen.

Multi-ingredient Preparations. *Austral.*: Broncafect; *Austria*: Asthmatee EF-EM-ES; Gallen- und Lebertee St Severin; Hustensaft Weleda; *Canad.*: Echinamide Cold and Cough†; Honey Blend Herbal Cough Syrup; Honey Herb Cough Drops†; Original Herb Cough Drops†; Swiss Herb Cough Drops; *Cz.*: Original Schwedenbitter; Species Cholagogae Planta†; The Salvat; Zlucnikova Cajova Smes; *Ger.*: Weleda Hustenelixier; *Hung.*: Antipoll; *Ital.*: Altuss; Broncosedina; Broncosedina; *Pol.*: Amarosal; *S.Afr.*: Cough Elixir†; *Switz.*: Elixir contre la toux†; Hederix; *UK*: Allens Chesty Cough; Asthma & Catarrh Relief; Catarrheeze; Chest Mixture; Cough Soother Herbal Syrup; Cougheeze; Herb and Honey Cough Elixir; Honey & Molasses; Horehound and Aniseed Cough Mixture; Horehound Plus Cough Syrup; Modern Herbals Cough Mixture; Vegetable Cough Remover.

Homoeopathic Preparations. *Canad.*: Infilex†; *Neth.*: Infragil; *UK*: Cough Elixir.

Mecysteine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de mecisteína; Mecisteína, hidrocloruro de; Mécystéine, Chlorhydrate de; Mecysteini Hydrochloridum; Methyl Cysteine Hydrochloride; Methylcysteine Hydrochloride; Мецистеина Гидрохлорид.

Methyl L-2-amino-3-mercaptopropionate hydrochloride.

$C_4H_9NO_2S,HCl$=171.6

CAS — 2485-62-3 (mecysteine); 18598-63-5 (mecysteine hydrochloride); 5714-80-7 (mecysteine hydrochloride).

UNII — 33RG619160.

Uses and Administration

Mecysteine hydrochloride is used as a mucolytic in respiratory disorders associated with productive cough (p. 1651.2). It is given orally in a usual dose of 200 mg three times daily before meals reduced to 200 mg twice daily after 6 weeks. A rapid clinical effect can be achieved by giving 200 mg four times daily for the first 2 days. For doses in children, see below.

Mecysteine has also been given by inhalation.

Administration in children. The recommended oral dose of mecysteine hydrochloride in children aged 5 to 12 years is 100 mg 3 times daily.

Respiratory disorders. Mecysteine hydrochloride given orally has reduced symptoms of cough in patients with chronic bronchitis or other respiratory disorders, but its effect on sputum production and pulmonary function has been variable.[1,2] The use of mucolytics in chronic obstructive pulmonary disease (p. 1199.1) is controversial.

1. Aylward M, *et al.* Clinical therapeutic evaluation of methylcysteine hydrochloride in patients with chronic obstructive bronchitis: a balanced double-blind trial with placebo control. *Curr Med Res Opin* 1978; 5: 461–71.
2. Sahay JN, *et al.* The effect of methyl cysteine (Visclair) in respiratory diseases: a pilot study. *Clin Trials J* 1982; 19: 137–43.

Adverse Effects and Precautions

Nausea and heartburn have occasionally been reported. Since mucolytics may disrupt the gastric mucosal barrier mecysteine hydrochloride should be used with caution in patients with a history of peptic ulcer disease.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Visclair†; *UK*: Visclair.

Menglytate *(rINN)*

Menglitato; Menglytatum; Menthol Ethylglycolate; Менглитат.

p-Menth-3-yl ethoxyacetate.

$C_{14}H_{26}O_3$=242.4

CAS — 579-94-2.

UNII — C3B9R0E116.

Profile

Menglytate is an ingredient of some preparations promoted for the treatment of cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Coryfin C; Neo Borocillina Balsamica; Neo Borocillina Decong.

Methoxyphenamine Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de metoxifenamina; Methoxiphenadrin Hydrochloride; Méthoxyphénamine, Chlorhydrate de; Methoxyphenamini Hydrochloridum; Metoxifenamina, hidrocloruro de; Mexyphamine Hydrochloride; Метоксифенамина Гидрохлорид.

2-Methoxy-*N*α-dimethylphenethylamine hydrochloride.

$C_{11}H_{17}NO,HCl$=215.7

CAS — 93-30-1 (methoxyphenamine); 5588-10-3 (methoxyphenamine hydrochloride).

ATC — R03CB02.

ATC Vet — QR03CB02.

UNII — 52V8BVV7FX.

Profile

Methoxyphenamine is a sympathomimetic with effects similar to those of ephedrine (p. 1663.1), given orally as the hydrochloride. It has been used as a bronchodilator mainly in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Cheracol; *China*: Asmeton (阿斯美); Ke Zhi (克之); *Hong Kong*: Asmeton; *Irl.*: Casacol; *Venez.*: Metoxifillin.

Methyl Dacisteine *(rINNM)*

Dacisteína de metilo; Dacistéine Méthyle; Dacisteinum Methylis; EL-1035 (dacisteine); Methyl Diacetylcysteinate; Дацистеин Метил.

Methyl *N*,*S*-diacetyl-L-cysteinate.

$C_8H_{13}NO_4S$=219.3

CAS — 18725-37-6 (dacisteine); 19547-88-7 (methyl dacisteine).

Profile

Like acetylcysteine (p. 1652.2), methyl dacisteine has been used as a mucolytic in respiratory disorders associated with productive cough (p. 1651.2). It has been given orally in a usual dose of 600 mg daily, divided into 3 or 4 doses.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Mucothiol.

Methylephedrine Hydrochloride *(BANM)* ⊗

dl-N-Methylephedrine Hydrochloride; *dl*-Methylephedrine Hydrochloride; Metilefedrina, hidrocloruro de; Метилэфедрина Гидрохлорид.

(1*RS*,2*RS*)-2-Dimethylamino-1-phenylpropan-1-ol hydrochloride.

$C_{11}H_{17}NO,HCl$=215.7

CAS — 552-79-4 ((-)-methylephedrine); 1201-56-5 ((±)-methylephedrine); 38455-90-2 ((-)-methylephedrine hydrochloride); 942-46-1 ((±)-methylephedrine hydrochloride); 18760-80-0 ((±)-methylephedrine hydrochloride).

UNII — 99214P83XM.

Pharmacopoeias. In *Jpn*.

Profile

Methylephedrine hydrochloride is a sympathomimetic with effects similar to those of ephedrine (p. 1663.1). It has been used as a bronchodilator and is given orally in combination preparations for the relief of cough and nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Kang Yu Deng Tong (康裕登通).

Multi-ingredient Preparations. *China*: Ai Kai Ping (爱凯平); Norpin A (纳尔平); Xi Er Ke (西尔克); *Hong Kong*: Codaewon; *Jpn*: Colgen Kowa IB; Lightgen; Sin Colgen Kowa Kaze†; *S.Afr.*: Ilvico†; *Switz.*: Tossamine plus; *Thai.*: Hustazol-C; Methorcon; *Venez.*: Ilvico.

Morclofone *(rINN)*

Dimeclofenone; Morclofona; Morclofonum; Morclophon; Морклофон.

4′-Chloro-3,5-dimethoxy-4-(2-morpholinoethoxy)benzophenone.

$C_{21}H_{24}ClNO_5$=405.9

CAS — 31848-01-8 (morclofone); 31848-02-9 (morclofone hydrochloride).

ATC — R05DB25.

ATC Vet — QR05DB25.

UNII — VY62TIB872.

Profile

Morclofone is a centrally acting cough suppressant used for non-productive cough (p. 1651.2); it is given orally in usual doses of 150 mg four or five times daily. It has also been given as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Nitux.

Naphazoline *(BAN, rINN)* ⊗

Nafatsolilni; Nafazolin; Nafazolina; Naphazolinum; Нафазолин.

2-(1-Naphthylmethyl)-2-imidazoline.

$C_{14}H_{14}N_2$=210.3

CAS — 835-31-4.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — H231GF118V.

Naphazoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de nafazolina; Nafatsolilnihydrokloridi; Nafazolin Hidroklorür; Nafazolina, hidrocloruro de; Nafazolin-hidroklorid; Nafazolin-hydrochlorid; Nafazolinhydroklorid; Nafazolino hidrochloridas; Naphazoline, Chlorhydrate de; Naphazolinhydrochlorid; Naphazolini Hydrochloridum; Нафазолина Гидрохлорид.

$C_{14}H_{14}N_2,HCl$=246.7

CAS — 550-99-2.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — MZ1131787D.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Naphazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water; soluble in alcohol. Protect from light.

USP 36: (Naphazoline Hydrochloride). A white, odourless, crystalline powder. Freely soluble in water and in alcohol; very slightly soluble in chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Naphazoline Nitrate *(BANM, rINNM)* ⊗

Nafatsoliinitraatti; Nafazolin Nitrat; Nafazolina, nitrato de; Nafazolinnitrat; Nafazolin-nitrát; Nafazolino nitratas; Nafazoliny azotan; Naphazoline, Nitrate de; Naphazolini nitras; Naphazolinium Nitricum; Naphazolinnitrat; Naphthizinum; Nitrato de nafazolina; Нафазолина Нитрат.

$C_{14}H_{14}N_2,HNO_3$=273.3

CAS — 5144-52-5.

ATC — R01AA08; R01AB02; S01GA01.

ATC Vet — QR01AA08; QR01AB02; QS01GA01.

UNII — SC99GR1T5S.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *Viet*.

Ph. Eur. 8: (Naphazoline Nitrate). A white or almost white, crystalline powder. Sparingly soluble in water; soluble in alcohol. A 1% solution in water has a pH of 5.0 to 6.5. Protect from light.

Uses and Administration

Naphazoline is a sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor with a rapid and prolonged action in reducing swelling and congestion when applied to mucous membranes.

Naphazoline and its salts are used for the symptomatic relief of nasal congestion (p. 1652.1). Solutions containing 0.05 to 0.1% of the hydrochloride or the nitrate may be applied topically as nasal drops or a spray usually up to once every 6 hours. For doses in children, see below.

Solutions containing up to 0.1% of naphazoline hydrochloride have been instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Naphazoline has been used as a vasoconstrictor with local anaesthetics.

Naphazoline acetate has also been used in nasal preparations.

Administration in children. In some countries, solutions containing naphazoline nitrate 0.05% have been applied topically as nasal drops or a spray, usually 2 or 3 times daily, in children aged 7 years and over for the symptomatic relief of nasal congestion.

Adverse Effects, Treatment, and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; naphazoline has mainly alpha-agonist effects. After local use, transient irritation may occur. Rebound congestion may occur after frequent or prolonged use. Systemic effects, including nausea, headache, and dizziness, have occurred after topical use. Overdosage or accidental oral use of naphazoline may cause CNS depression with marked reduction of body temperature and bradycardia, sweating, drowsiness, and coma, particularly in children; it should be used with great caution, if at all, in infants and young children. Use of naphazoline in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Hypertension may be

followed by rebound hypotension. Treatment of adverse effects is symptomatic.

Abuse. Ischaemic stroke that developed in a 46-year-old man was considered to have been precipitated by abuse of topical naphazoline.[1] The patient had used more than 20 nasal applications daily for several years.

1. Costantino G, *et al.* Ischemic stroke in a man with naphazoline abuse history. *Am J Emerg Med* 2007; 25: 983.e1–983.e2.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing naphazoline, see under Phenylephrine, p. 1673.2.

Intraoperative use. A report[1] of 2 cases of toxicity associated with intraoperative use of a naphazoline-soaked sponge to control excessive bleeding after adenoidectomy. Hypertension and reflex bradycardia, which evolved in one case into marked hypotension, were noted in both patients. There was evidence of CNS depression with a reduced respiration rate and prolonged recovery from anaesthesia.

1. Wenzel S, *et al.* Course and therapy of intoxication with imidazoline derivate naphazoline. *Int J Pediatr Otorhinolaryngol* 2004; 68: 979–83.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies naphazoline for ophthalmic use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Since naphazoline is absorbed through the nasal mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Pharmacokinetics

Systemic absorption has been reported after topical use of solutions of naphazoline. It is not given systemically, but it is readily absorbed from the gastrointestinal tract. Naphazoline instilled into the eye causes conjunctival vasoconstriction within 10 minutes and effects can last for up to 6 hours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Actifedrin Nasal; Afluhist; Bactio Rhin; Bano Ocular Agrand†; Dazolin; Disel; Fabozolina; Gentisyl NF; Gotabiotic D; Gotinal; Let-Nasal; Mirasan; Mirus-S; Nafazolex; Nasalex; Panoptic NF; Privina; Rhinal; *Austral.*: Albalon; Murine Clear Eyes; Naphcon; *Austria*: Aconex; Coldan; Rhinon; Rhinoperd; *Belg.*: Deltarhinol-Mono; Naphcon; Neofenox Naphazoline†; Neusinol; Priciasol; Vasocedine; *Braz.*: Claroft; Gotaliv; Multisoro; Narix; Nazicol†; Neosoro; Privina; Rinomax; Rinos-A; Sonarin (AD); Soroclim; *Canad.*: Ak-Con; Albalon; Allergy Drops†; Clear Eyes; Diopticon; Naphcon Forte; Original Eye Drops; Refresh Redness Relief; *Chile*: Clarimir; Red Off; *China*: Hu Tai (呼泰); Runjie (润洁); *Cz.*: Sanorin; *Ger.*: Duraultra N; Privin†; Proculin†; Tele-Stulln†; Televis-Stulln; *Gr.*: Coldan; Naphcon; *Hong Kong*: Albalon; All Clear; *Hung.*: Iridina; *India*: Clearine; Ocucel; Ocustress; *Indon.*: Optrine†; *Irl.*: Albalon†; Murine Irritation and Redness Relief; *Israel*: Naphcon Forte†; *Ital.*: Collirio Alfa; Imidazyl; Iridina Due; Naftazolina; Pupilla; Rinazina; *Malaysia*: Albalon†; *Mex.*: Afazol; Alfazina; Alphadinal†; Celunaf; Fazolin; Gamatropin†; Gotinal; Nazil; Oftaseptic; *Neth.*: Albalon†; *NZ*: Clear Eyes; Naphcon; *Philipp.*: Cosooth; Vasoclear; *Pol.*: Rhinazin; *Rus.*: Nafazol (Нафазол); Sanorin (Санорин); *S.Afr.*: Murine Clear Eyes; Safyr Bleu; *Spain*: Alfa†; Miraclar; Vasoconstrictor Pensa; *Thai.*: Albalon; Naphcon†; *Turk.*: Deltarhinol†; Enfluclide†; *UK*: Murine Irritation & Redness Relief; *Ukr.*: Nasolin (Назолин)†; Sanorin (Санорин); *USA*: Advanced Eye Relief Redness; Ak-Con; Albalon†; All Clear†; Clear Eyes Plus Redness Relief; Clear Eyes; Napha Forte; Naphcon; Privine; *Venez.*: Clarasol; Clearize; Fazolan; Gotinal; Naphcon; Nas; Niazol; Ninazo.

Multi-ingredient Preparations. *Arg.*: Afluhist Plus; Alvo Nasal; Antibiocort; Bactio Rhin Prednisolona; Bideon; Biotaer Nasal†; Dexalergin; Disel Hidrocortisona; Drynisan; Factioneye; Fadanasal; Gripace; Hyalcrom; Mira Klonal; Mirus; Nasojol; Nasomicina; Neo-Currino; Neodexa Plus†; Neoefodil; Neosona; Nexadron Compuesto; Nexadron Plus; Panoptic; Provacsin Nasal; Refenax Colirio; Refenax Gotas Nasales; Rinofilax AG M; Rinogel; Rinolabsa; Suavithiol†; Vistadex; Visuclar; *Austral.*: Albalon-A; Antistine-Privine; Naphcon-A; Optrex Medicated†; Visine Allergy; *Austria*: Coldistan; Coldophthal; Luuf-Nasenspray; Ophtaguttal; Rhinon; Rhinoperd comp; *Belg.*: Minhavez; Naphcon-A; Sofraline; Sofrasolone; *Braz.*: Clanistil; Claril; Colirio Legrand; Colirio Moura Brasil; Colirio Teuto; Conidrin; Cristalin; Fluo-Vaso; Hemodotti†; Hidrocin; Lerin; Maxibell; Naridrin; Nariflux; Nasomil; Neo Quimica Colirio†; Nitrileno; Novo Rino; Rhinosept†; Rinisone; Sinustrat Vasoconstritor; Sorine Adulto; Stilux; Visazul; Visiplex; Visolon; Visual; Zincolok; *Canad.*: Albalon-A; Blue Collyrium; Clear Eyes Allergy; Clear Eyes for Dry Eyes Plus Redness Relief; Collyre Bleu Laiter; Diopticon A; Naphcon-A; Onrectal†; Opcon-A; Refresh Eye Allergy Relief; Visine Advance Allergy; Zincfrin-A†; *Chile*: Clarimir P; Dessolets; Miral; Naphcon-A; Naphtears; Nico Drops; Novo-Tears; Oculosan†; Oftallrio; Red Off Aqua; Red Off Plus; *China*: Naphcon-A (那赛达); Xin Le Dun (新乐敦); *Cz.*: Sanorin-Analergin; *Denm.*: Ansal†; Antistina-Privin; Sesal; *Fr.*: Collyre Bleu; Derinox; *Ger.*: Antistin-Privin†; duraultra†; Oculosan N†; Siozwo†; *Gr.*: Neo-Priphen; Oculosan; Septobore; Zabysept; Zincfrin-A; *Hong Kong*: Clear Blue; Frazoline†; Konjunktival; Naphcon-A; Nazin; Oculosan; Opcon-A; Vista-Tone†; Visurex; *India*: Andre-I-Kul†; Andre; Betnesol-N Nasal†; E-Norm; Efcorlin; Exxon; Penox†; I-Boric; I-Top; Igardex; Mezol; Microsol; Mil; N-Cool; N-Zolin; Naflin; NCZ; Nefacool; Nilhist; NPBor; Ocucel-A; Ocuclear; Ocudecon; Ocurest-AH; Ocurest-Z; Ocurest; Ovisil; Proto-Boric†; *Indon.*: Flamergi; Indofrin-A†; Isotic Azora; Naphcon-A; Oculosan; Zincopto; *Irl.*: Optrex Clear Eyes; *Israel*: Alnase; Optryl; Phenyphrine-Azol†; Proaf†; *Ital.*: Alfaflor; Antisettico Astringente Sedativo: Antistin-Privina; Collirio Alfa Antistaminico; Deltarinolo; Fotofil; Genalfa†; Imidazyl Antistaminico; Indaco; Iristamina; Oftalmil; Pupilla Antistaminico; Rinocidina; Zinc-Imizol; *Malaysia*: Alergoftal†; Napha A; Naphcon-A; *Mex.*: Afazol Z; Biofrin; Biotarson O†; Eyrasil; Istasol; Midazol Ofteno; Mirus; Naphacel; Naphtears; Opcon-A; Poentobral D; Soltrictor con Lagrifilm; Solutina; Sulvi; Zincfrin-A; *NZ*: Betnesol Aqueous; Clear Eyes ACR; Naphcon-A; Optrex Red-Eye Relief; Visine Allergy; *Philipp.*: Decocon A; Irazol; Moisturizing All Clear; Naphcon-A; Oculosan; Optaphen; Vistallerg; *Pol.*: Betadrin; Cincol; Dermophenazol; Mibalin†; Oculosan; Oftophenazol; Rhinophenazol; Sulfarinol; *Port.*: Alergiftalmina; *Rus.*: Betadrin (Бетадрин); Ocumethyl (Окуметил); Polynadim (Полинадим); Sanorin (Санорин); Sanorin-Analergin (Санорин-аналергин); *S.Afr.*: Adco-Nasdro†; Antistin-Privin; Covomycin; Covosan†; ENT; Fenox; Oculosan; Universal Nasal Drops†; Zincfrin-A†; *Singapore*: Antistin-Privin; Naphcon-A; Nazal Spray; *Spain*: Alergoftal; Centilux; Cloram Zinc†; Colirio-cilina Adren Astr†; Epistaxol; Kanafosal Predni†; Kanafosal†; Oftalmol Ocular; Ojosbel Azul†; Ojosbel; Rinovel†; Zolina; *Swed.*: Antasten-Privin†; *Switz.*: Antistin-Privin†; Collyre Bleu Laiter; Oculosan; Spray nasal comp pour adultes†; *Thai.*: Levoptin; Naphcon-A; Oculosan; *Turk.*: Alergoftal; Sulfarhin; *UK*: Eye Dew; Murine Bright & Moist Eyes; Optrex Red Eyes; *Ukr.*: Sanorin-Analergin (Санорин-Аналергин); *USA*: 4-Way Fast Acting; Antazoline-V; Clear Eyes Seasonal Relief; Maximum Strength Allergy Drops; Naphazoline Plus†; Naphcon-A; Naphopic-A; Ocuhist; Opcon-A; VasoClear A; Vasocon-A; Visine-A; *Venez.*: Camolyn Plus; Pinazo; Soltin; Soluclear.

Used as an adjunct in:. *Fr.*: Xylocaine; *Spain*: Anestesico.

Pharmacopoeial Preparations
USP 36: Naphazoline Hydrochloride and Pheniramine Maleate Ophthalmic Solution; Naphazoline Hydrochloride Nasal Solution; Naphazoline Hydrochloride Ophthalmic Solution.

Neltenexine *(rINN)*

Neltenexina; Nelténexine; Neltenexinum; Нелтенексин.
4′,6′-Dibromo-α-[(*trans*-4-hydroxycyclohexyl)amino]-2-thiophene-carboxy-o-toluidide.
$C_{18}H_{20}Br_2N_2O_2S$=488.2
CAS — 99453-84-6.
ATC — R05CB14.
ATC Vet — QR05CB14.
UNII — U942DGM90X.

Profile

Neltenexine is a mucolytic that has been used in respiratory disorders associated with productive cough (p. 1651.2). It has been given orally as the monohydrate, in usual doses of 37.4 mg three times daily. Neltenexine has also been given rectally as the hydrochloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Alveoten; Tenoxol†.

Nepinalone *(rINN)*

Nepinalona; Népinalone; Nepinalonum; Непиналон.
(±)-3,4-Dihydro-1-methyl-1-(2-piperidinoethyl)-2(1*H*)-napthalenone.
$C_{18}H_{25}NO$=271.4
CAS — 22443-11-4.
ATC — R05DB26.
ATC Vet — QR05DB26.
UNII — L9806LPR7G.

Profile

Nepinalone has been used as the hydrochloride as a cough suppressant in non-productive cough (p. 1651.2). Oral doses of nepinalone hydrochloride 10 mg have been given three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Nepituss; Placatus; Tussol ina.

Nicocodine *(BAN, rINN)*

Nicocodina; Nicocodinum; Никокодин.
6-Nicotinoylcodeine; 3-*O*-Methyl-6-*O*-nicotinoylmorphine.
$C_{24}H_{24}N_2O_4$=404.5
CAS — 3688-66-2.
UNII — DYX391P13E.

Profile

Nicocodine is an opioid related to codeine (p. 40.2). It has been used orally as the hydrochloride for its central cough suppressant effects in non-productive cough.

Normethadone Hydrochloride *(BANM, rINNM)*

Desmethylmethadone Hydrochloride; Hidrocloruro de normetadona; Hoechst-10582 (normethadone); Normetadona, hidrocloruro de; Norméthadone, Chlorhydrate de; Normethadoni Hydrochloridum; Phenyldimazone Hydrochloride; Норметадона Гидрохлорид.
6-Dimethylamino-4,4-diphenylhexan-3-one hydrochloride.
$C_{20}H_{25}NO,HCl$=331.9
CAS — 467-85-6 (normethadone); 847-84-7 (normethadone hydrochloride).
ATC — R05DA06.
ATC Vet — QR05DA06.

Profile

Normethadone is closely related to methadone (p. 88.3). The hydrochloride is given orally as a cough suppressant in preparations for non-productive cough.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Cophylac.

Noscapine *(BAN, rINN)*

L-α-Narcotine; Narcotine; Noscapin; Noscapina; Noscapinum; Noskapiini; Noskapin; Noskapinas; Noszkapin; NSC-5366; Носкапин.
(3*S*)-6,7-Dimethoxy-3-[(5*R*)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo[4,5-*g*]isoquinolin-5-yl]phthalide.
$C_{22}H_{23}NO_7$=413.4
CAS — 128-62-1.
ATC — R05DA07.
ATC Vet — QR05DA07.
UNII — 8V32U4AOQU.

Description. Noscapine is an alkaloid obtained from opium.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Noscapine). A white or almost white, crystalline powder or colourless crystals. Practically insoluble in water at 20 degrees, very slightly soluble at 100 degrees; slightly soluble in alcohol; soluble in acetone; dissolves in strong acids although the base may be precipitated on dilution with water. Protect from light.

USP 36: (Noscapine). A fine, white or practically white, crystalline powder. Practically insoluble in water; slightly soluble in alcohol and in ether; soluble in acetone; freely soluble in chloroform.

Noscapine Camsilate *(BANM, rINNM)*

Camphoscapine; Camsilato de noscapina; Noscapina, camsilato de; Noscapine, Camsilate de; Noscapine Camsylate; Noscapini Camsilas; Носкапина Камзилат.
Noscapine camphor-10-sulphonate.
$C_{22}H_{23}NO_7$, $C_{10}H_{16}O_4S$=645.7
CAS — 25333-79-3.
ATC — R05DA07.
ATC Vet — QR05DA07.

Noscapine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de noscapina; Narcotine Hydrochloride; Noscapina, hidrocloruro de; Noscapine, Chlorhydrate de; Noscapinhydrochlorid-Monohydrat; Noscapini Hydrochlor-

idum; Noscapini Hydrochloridum Monohydricum; Noscapinium Chloride; Noskapiinhydrokloridi; Noskapin hydrochlorid monohydrát; Noskapinhydroklorid; Noskapino hidrochloridas; Noskapiny chlorowodorek; Noszkapinhidroklorid; Носкапина Гидрохлорид.

$C_{22}H_{23}NO_7.HCl.H_2O$=467.9

CAS — 912-60-7 (anhydrous noscapine hydrochloride).

ATC — R05DA07.

ATC Vet — QR05DA07.

UNII — TTN62ITH9I.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* (both with H_2O); in *Jpn* (with xH_2O).

Ph. Eur. 8: (Noscapine Hydrochloride). A white or almost white, hygroscopic, crystalline powder or colourless crystals. Freely soluble in water and in alcohol. Aqueous solutions are faintly acid; the base may be precipitated when the solutions are allowed to stand. A 2% solution in water has a pH of not less than 3.0. Protect from light.

Uses and Administration

Noscapine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p. 1660.2). It is given in an oral dose of up to 50 mg three times daily. It is also used rectally. Noscapine has also been given as the ascorbate, camsilate, embonate, and the hydrochloride.

Adverse Effects and Precautions

As for Dextromethorphan, p. 1660.3. Hypersensitivity reactions have been reported.

Breast feeding. Maximum concentrations of noscapine in the breast milk of 8 women given 100 or 150 mg of noscapine ranged[1] from 11 to 83 nanograms/mL. It was estimated that breast-fed infants of mothers receiving noscapine 50 mg three times daily would ingest at most 300 nanograms/kg of noscapine per feed, an amount considered unlikely to be a hazard. No adverse effects have been seen in breast-fed infants whose mothers were given noscapine, and the American Academy of Pediatrics[2] considers that it is therefore usually compatible with breast feeding.

1. Olsson B, *et al.* Excretion of noscapine in human breast milk. *Eur J Clin Pharmacol* 1986; 30: 213–15.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 13/12/06)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies noscapine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Pregnancy. The UK CSM stood by their recommendation[1] that products containing noscapine should be contra-indicated in women of child-bearing potential (because of potential mutagenic effects[2]), after criticism that the decision was based solely on the results of *in-vitro* work.[3]

1. Asscher AW, Fowler LK. Papaveretum in women of childbearing potential. *BMJ* 1991; 303: 648.
2. CSM. Genotoxicity of papaveretum and noscapine. *Current Problems* 31 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024449&RevisionSelectionMethod=LatestReleased (accessed 21/03/07)
3. Allen S, *et al.* Papaveretum in women of child bearing potential. *BMJ* 1991; 303: 647.

Interactions

Noscapine should not be given with alcohol or other CNS depressants.

Anticoagulants. For mention of a possible interaction between noscapine and *warfarin*, see Cough Suppressants, p. 1533.2.

Pharmacokinetics

References.

1. Karlsson MO, *et al.* Pharmacokinetics of oral noscapine. *Eur J Clin Pharmacol* 1990; 39: 275–9.
2. Karlsson MO, Dahlstrom B. Serum protein binding of noscapine: influence of a reversible hydrolysis. *J Pharm Pharmacol* 1990; 42: 140–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Nosca-Mereprine; Noscaflex; *Ger.*: Capval; *Hong Kong*: Excopin†; Recoma†; *Indon.*: Longatin; Mercotin; *Neth.*: Fluitussin; Kruidvat Hoestdrank Noscapine; Natterman Noscasan; Otrivin; Roter Noscapect; *S. Afr.*: Nitepax; *Spain*: Tuscalman; *Swed.*: Nipaxon; *Switz.*: Tussanil N.

Multi-ingredient Preparations. *Arg.*: Funciobron; Graneodin N; No-Tos Pocket; Tosedrin Compuesto†; Vi-Balsabron; *Austria*: Tuscalman; Tuscalman; *Belg.*: Noscaflex; *Chile*: AB Antitusivo; Bucogerm Tos; Captus†; Congestex; Cotibin Flu Dia y Noche; Freshmel Tos; Geniol Compuesto; Geniol-P Compuesto con Clorfenamino†; Graneodin-Tos; Gripexin Limonada Caliente†; No-Flu; Tapsin Compuesto con Clorfenamina; Tapsin Compuesto Dia/Noche Plus; Tapsin Compuesto DN; Tapsin Compuesto; *China*: Asmeton (阿斯美); Ke Zhi (克之); *Fr.*: Tussisedal; *Hong Kong*: Asmeton; Coldcap-A; Coldtab-2; Coltalin-GP Extra; Coughlin†; Decaugh II†; Dr Jacobson Cough Syrup†; Nosazine†; Nosbrom†; Noscaphylline†; Panadol Cold & Flu Extra; Wel-Coplex†; *India*: Coscopin Plus; Coscopin; Coscopin; *Indon.*: Dextrosin Anak; Flucodin; Flunadin†; Noscapax; Paratusin; Paratusin; Tilomix; *Singapore*: New Tonin Troche; Tonin Cough; *Swed.*: Spasmofen; *Switz.*: DemoTussil; Hederix; Spasmosol†; Tossamine plus; Tossamine; Tuscalman; Tuscalman; *Turk.*: Coldeks; Tusifon.

Oxeladin Citrate *(BANM, rINNM)*

Citrato de oxeladina; Okseladiinivetysitraatti; Okseladinovandenilio citratas; Oxeladina, citrato de; Oxeladin-citrát; Oxéladine, Citrate d'; Oxéladine, hydrogénocitrate d'; Oxeladini Citras; Oxeladini hydrogenocitras; Oxeladinvätecitrat; Окселадина Цитрат.

2-(2-Diethylaminoethoxy)ethyl 2-ethyl-2-phenylbutyrate dihydrogen citrate.

$C_{20}H_{33}NO_3.C_6H_8O_7$=527.6

CAS — 468-61-1 (oxeladin); 52432-72-1 (oxeladin citrate).

ATC — R05DB09.

ATC Vet — QR05DB09.

UNII — 5AEV5C340C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Oxeladin Hydrogen Citrate). A white or almost white, crystalline powder. It exhibits polymorphism. Freely soluble in water; slightly to very slightly soluble in ethyl acetate.

Profile

Oxeladin citrate has been given orally as a centrally acting cough suppressant for non-productive cough (p. 1651.2). Up to 50 mg daily in divided doses has been given orally. Higher doses of up to 120 mg daily have been given as a modified-release preparation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elitos; Frenotos; Nadetos; Plardox; *Fr.*: Paxeladine; *Gr.*: Antivix; *Ukr.*: Paxeladin (Пакселадин).

Multi-ingredient Preparations. *Arg.*: Aseptobron Bromexina; Aseptobron C; Frenotos Muc; Pectoral Lafedar; *Mex.*: Connex; Fluxedan; Tesalon Tenalif; TheraFlu Tenalif.

Oxolamine *(rINN)*

683-M; Oksolamiini; Oksolamin; Oxolamin; Oxolamina; Oxolaminum; Оксоламин.

5-[2-(Diethylamino)ethyl]-3-phenyl-1,2,4-oxadiazole.

$C_{14}H_{19}N_3O$=245.3

CAS — 959-14-8.

ATC — R05DB07.

ATC Vet — QR05DB07.

UNII — 90BEA145GY.

Oxolamine Citrate *(rINNM)*

AF-438; Citrato de oxolamina; Oxolamina, citrato de; Oxolamine, Citrate d'; Oxolamini Citras; SKF-9976; Оксоламина Цитрат.

$C_{14}H_{19}N_3O.C_6H_8O_7$=437.4

CAS — 1949-20-8.

ATC — R05DB07.

ATC Vet — QR05DB07.

UNII — K5X4XBR694.

Oxolamine Phosphate *(rINNM)*

Fosfato de oxolamina; Oxolamina, fosfato de; Oxolamine, Phosphate d'; Oxolamini Phosphas; Оксоламина Фосфат.

CAS — 1949-19-5.

ATC — R05DB07.

ATC Vet — QR05DB07.

Profile

Oxolamine is a cough suppressant with a mainly peripheral action that has been used for non-productive cough (p. 1651.2). It has been given as the citrate in usual oral doses of 100 to 200 mg three times daily. The phosphate has been used similarly. It has also been given as the tannate.

Hallucinations in children have been reported after oxolamine use.

References.

1. McEwen J, *et al.* Hallucinations in children caused by oxolamine citrate. *Med J Aust* 1989; 150: 449–52.

Interactions. *ANTICOAGULANTS.* For mention of a possible interaction between oxolamine and *warfarin*, see Cough Suppressants, p. 1533.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Numosol; Perebron; Respibron; Teratos; Tulox; *Gr.*: Goltuss; Perebron; *Israel*: Symphocal; *Ital.*: Tussibron; *Mex.*: Aledron; Bredon; Contuxin†; Eumol; Expecmin; Oxathos; Oxobron†; Oxomar; Oxomifer; Oxotus†; Oxotusin; *Turk.*: Kalamin; Oksabron; Oksalamin; Oxotuss; Perbrons; Perebron; Sekodin; Subitol; Tusebron; *Venez.*: Broxol; Cafox; Calcimonio; Citralamina; Lexo; Opilina; Oxalcor; Oxotil; Perebron.

Multi-ingredient Preparations. *Ital.*: Uniplus; *Mex.*: Caltusine; Caobe; Guaxoquim; Otofen; *Turk.*: Contex; Forza; Katarin Forte; Katarin; Oledro; *Venez.*: Opilina Compuesta; Oxolavin Compuesto.

Oxymetazoline Hydrochloride

(BANM, USAN, rINNM) ⊗

HI-990; Hidrocloruro de oximetazolina; Oksimetatsoliinihydrokloridi; Oksimetazolin Hidroklorür; Oksimetazolino hidrochloridas; Oximetazolina, hidrocloruro de; Oximetazolinhidroklorid; Oxlmetazolinhydroklorid; Oxymetazolin hydrochlorid; Oxymétazoline, chlorhydrate d'; Oxymetazolinhydrochlorid; Oxymetazolini Hydrochloridum; Sch-9384; Оксиметазолина Гидрохлорид.

$C_{16}H_{24}N_2O.HCl$=296.8

CAS — 2315-02-8.

ATC — R01AA05; R01AB07; S01GA04.

ATC Vet — QR01AA05; QR01AB07; QS01GA04.

UNII — K89MJ05SVY.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Oxymetazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 36: (Oxymetazoline Hydrochloride). A white to practically white, fine, hygroscopic, crystalline powder. Soluble 1 in 6.7 of water, 1 in 3.6 of alcohol, and 1 in 862 of chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 4.0 and 6.5. Store in airtight containers.

Uses and Administration

Oxymetazoline is a direct-acting sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor and reduces swelling and congestion when applied to mucous membranes. It acts within a few minutes and the effect lasts for up to 12 hours. It is used as the hydrochloride for the symptomatic relief of nasal congestion (p. 1652.1). In adults and children aged over 6 years, a 0.05% solution of oxymetazoline hydrochloride is applied topically as nasal drops or a spray, usually 2 or 3 times daily to each nostril as required. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including oxymetazoline) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

A 0.025% solution of oxymetazoline hydrochloride may be instilled into the eye every 6 hours when necessary as a conjunctival decongestant in adults and children aged over 6 years (see Conjunctivitis, p. 611.1).

Administration in children. For details of the use of oxymetazoline hydrochloride in children, see Uses and Administration, above.

Adverse Effects, Treatment, and Precautions

As for Naphazoline, p. 1669.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies oxymetazoline for

nasal use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

Since oxymetazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Apracur Nasal; Lidil; Newclar; Rinox VX; Visine D; Yusin; *Austral.*: Chemists Own Decongestant Nasal Spray; Dimetapp 12 Hour Nasal; Drixine Nasal; Logicin Rapid Relief; Sudafed Nasal Decongestant; Vicks Sinex; *Austria*: Nasiben; Nasivin; *Belg.*: Nesivine; Rhino Humexť; Vicks Sinex; *Braz.*: Afrin; Aturgyl; Desfrin; Freenal; Nasivin; Oxifrin; Rinidal; *Canad.*: Afrinť; Claritin Allergic Congestion Relief; Claritin Eye Allergy Relieft; Decongestant Nasal Mist; Dristan; Drixoral; Long Lasting Nasal Mist; Vicks Sinex; Visine Workplace; Zicam Congestion Relieft; Zicam Sinus Reliefť; *Chile*: Facimin; Iliadin; Oxilin; *China*: Da Fen Lin (达芬霖); Dan Zhong Di Bi Ye (丹中滴鼻液); Di Li Tuo (迪立托); Feng Lang (风朗); Oxylin (欧斯林); *Cz.*: Nasivin; Oxamet; Sinex Vicks; *Denm.*: Iliadinť; *Fin.*: Vicks Sinex; *Fr.*: Aturgyl; Pernazene; *Ger.*: Nasivin Sanftť; Nasivin; Vistoxynť; Wick Sinex; *Gr.*: Ezixin; Iliadin; Narol; Ronal; Vicks Vapospray; *Hong Kong*: Afrin; Durationť; Iliadin; Logicin Rapid Relief; Long Lasting Decongestant Nasal Mist; *Hung.*: Afrin; Nasivin; *India*: Naselin; Nasivion; Nazoden; Oxylin; Sinarest-PD; Sinarest; *Indon.*: Afrin; Iliadin; Visine LR; *Irl.*: Iliadinť; Oxylinť; Vicks Sinex; *Israel*: Af-Tipa; Alrin; Nasivin; Rhinoclir; Sinulen; *Ital.*: Actifed Nasale; Equimet; Ossimet; Oxilin; Rino Calyptol; *Jpn*: Nasivin; *Malaysia*: Afrin; Iliadin; Oxynase; *Mex.*: Afrinť; Iliadin; Naztril; Oxylin; Sinex; Visine AD; *Neth.*: Afrin; Nasivin; Oxylin; Vicks Sinex; *Norw.*: Iliadinť; Rhinox; *NZ*: At-Eze†; Dimetapp 12 Hour Nasal; *Philipp.*: Drixine; Nasivin; *Pol.*: Acatar; Afrin; Nasivin; Nosox; Oxalin; Resoxym; *Port.*: Alerjon; Bisolspray; Nasarox; Nasex; Nasorhinathiol; Oxylin; Rinerge; Sinexsensi; Vicks Vapospray; *Rus.*: Nasivin (Називин); Nazol (Назол); Nesopin (Несопин); Nokspray (Нокспрей); Sanorinchik (Саноринчик); *S. Afr.*: Allergex; DriNasal; Dristan; Drixine; Iliadin; Oxylin; Sparkling White Eye Drops†; Vicks Decongestant†; *Singapore*: Afrin; Iliadin; Nazolin; Oxy-Nase; Utabon†; *Spain*: Alerfrin; Antirrinum; Corilisina†; Couldespir; Cuvenax; Friresp; Lairesp; Nasolina; Nebulicina; Novag Rino; Nuerel; Oftinal†; Respibien; Respir; Serranasal†; SinexSensi; Utabon; *Swed.*: Iliadin; Nasin; Nezeril; Vicks Sinex; *Switz.*: Nasivine; *Thai.*: Iliadin; Metzodin; Oxymet; Pernazene Oxy; *Turk.*: Burazin; Iliadin; Oksinazal; Rinidin; *UAE*: Nasivin; *UK*: Afrazine; Nasivin; Vicks Sinex; *Ukr.*: Nasalong (Назалонг); Nasivin (Називин); Naso-Spray (Назо-Спрей); Nazol (Назол); Noxprey (Нокспрей); Oxamet (Оксамет)†; Rinazoline (Риназолин)†; Rint (Ринт); *USA*: 4-Way Long Lasting; Afrin Extra Moisturizing; Afrin Sinus; Afrin; Allerest 12 Hour Nasal†; Chlorphed-LA; Dristan 12-hr Nasal Decongestant Spray; Dristan Long Lasting; Duramist Plus; Duration; Genasal; Nasal Relief; Nasal Spray; Neo-Synephrine 12 Hour; Nostrilla Complete Congestion Relief; Nostrilla; NTZ Long Acting Nasal; Twice-A-Day; Vicks Sinex 12-Hour; Visine LR; *Venez.*: Afrin; Airfen; Clarix; Drixine; Nasin.

Multi-ingredient Preparations. *Arg.*: Alosol; Panoxi; *Austral.*: Nasext; *Austria*: Wick SinexAloe; *Fr.*: Deturgylone; *Ger.*: Nasivin Zinkť; *Hong Kong*: Bonjedex; *Hung.*: Nasopax; *Israel*: Sinaft; *Ital.*: Vicks Sinex; *Mex.*: Grimal; Hyalox; *NZ*: Vicks Sinext; *Rus.*: Nazol Advance (Назол Адванс); *S.Afr.*: Nazene Z; *Spain*: Respibien Antialergico; Seniospray†; Utabon Complex; Vicks Spray†; *Switz.*: Vicks Sinex; *Ukr.*: Nazol Advans (Назол Адванс).

Pharmacopoeial Preparations
USP 36: Oxymetazoline Hydrochloride Nasal Solution; Oxymetazoline Hydrochloride Ophthalmic Solution.

Pentoxyverine *(BAN, rINN)*

Carbetapentane; Pentoksiveriini; Pentoxiverin; Pentoxiverina; Pentoxyvérine; Pentoxyverinum; Пентоксиверин.
2-[2-(Diethylamino)ethoxy]ethyl 1-phenylcyclopentanecarboxylate.
$C_{20}H_{31}NO_3$=333.5
CAS — 77-23-6.
ATC — R05DB05.
ATC Vet — QR05DB05.
UNII — 32C726X12W.

Pentoxyverine Citrate *(BANM, rINNM)*

Carbetapentane Citrate; Citrato de pentoxiverina; Pentoksiveriinivetysitraatti; Pentoksiverino-vandenilio citratas; Pentoxiverina, citrato de; Pentoxiverin-hidrogén-citrát; Pentoxiverinvätecitrat; Pentoxyverincitrát; Pentoxyverin-citrát; Pentoxyvérine, Citrate de; Pentoxyverine Hydrogen Citrate; Pentoxyvérine, hydrogénocitrate de; Pentoxyverini Citras; Pentoxyverini Hydrogenocitras; UCB-2543; Пентоксиверина Цитрат.
$C_{20}H_{31}NO_3.C_6H_8O_7$=525.6
CAS — 23142-01-0.
ATC — R05DB05.
ATC Vet — QR05DB05.
UNII — 4SH0MFJ5HJ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.*

Ph. Eur. 8: (Pentoxyverine Hydrogen Citrate; Pentoxyverine Citrate BP 2014). A white or almost white crystalline powder. M.p. about 93 degrees. Freely soluble in water and in methyl alcohol; soluble in alcohol and in dichloromethane; very soluble in glacial acetic acid. A 10% solution in water has a pH of 3.3 to 3.7. Protect from light.

Pentoxyverine Hydrochloride *(BANM)*

Pentoksiverin Hidroklorür; Pentoxiverina, hidrocloruro de; Пентоксиверина Гидрохлорид.
$C_{20}H_{31}NO_3.HCl$=369.9
CAS — 1045-21-2.
ATC — R05DB05.
ATC Vet — QR05DB05.
UNII — MG7AT31IVT.

Profile

Pentoxyverine is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). Usual doses of up to 180 mg daily of the citrate or hydrochloride have been given orally in divided doses. The tannate is also given orally and the base has been given rectally.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pentoxyverine as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Nyal Dry Cough; *Austria*: Sedotussin†; *Belg.*: Balsoclase Antitussivum; *Fin.*: Toclase†; *Fr.*: Clarix Toux Seche; Codotussyl Toux Seche; Codotussyl Toux Seche; Toclase Toux Seche; Vicks Pectoral; *Ger.*: Sedotussin; Silomat; *Gr.*: Tuclase; *Hong Kong*: Toclase†; *Hung.*: Sedotussin†; *Ital.*: Tuclase†; *Neth.*: Balsoclase†; Tuclase†; *Philipp.*: Toclase; *Thai.*: Toclase†; *Turk.*: Toclase; *USA*: Solotuss†.

Multi-ingredient Preparations. *Arg.*: Bio Grip Plus; Wilpan Antigripal; *Austral.*: Vicks Cough Syrup†; *Braz.*: Coldrin; Resprin; *China*: Xiaoke (消咳); *Fin.*: Toclase Expectorant†; *Hong Kong*: Active Cough Syrup†; Against Cough†; Broncholax†; Coci-Fedra†; Cofetal†; Marflu-X†; Marsedyl D†; Vida Cough†; *Neth.*: Balsoclase Compositum†; Balsoclase-E†; *S.Afr.*: Vicks Acta Plus†; *Turk.*: Gayaben; Seskadeks; *USA*: Albatussin; Allres Pd†; AMBI 1000/5†; Aquatab C†; Aridex; BetaVent†; C-Tanna 12D; Carb Pseudo-Tan; Carbatab; Carbatuss; Corzall Plus; Corzall-PE; Corzall; D-Tann CD; Diphen Tann/ PE Tann/ CT Tann; Duratuss CS†; Dynex VR†; Dytan-AT; Dytan-CD†; Dytan-CS; Exall-D; Exall; Extratuss; Extendryl GCP; Gentex†; Levall 12; Levall; Oratuss; Pyrlex CB; Re-Tann; Rentamine Pediatric; Respi-Tann G†; Respi-Tann Pd; Rynatuss†; Tannic-12; Trexbrom; Tri-Tannate Plus Pediatric; Tuss-Tan; Tussi-12 D; Tussi-12; Tussi-12D S; Tussizone†; Tusso-ZMR†; Tusso-ZR†; Tustan 12S; V-Cof; Vazotan; XiraTuss; Xpect-AT; *Venez.*: Resprin; Tolmex; Yerba Santa.

Phenylephrine *(BAN, rINN)*

Fenilefrin; Fenilefrina; Fenilefrinas; Fenylefrin; Fenyyliefriini; Phenylephrin; Phényléphrine; Phenylephrinum; *m*-Synephrine; Фенилэфрин.
(1*R*)-1-(3-Hydroxyphenyl)-2-methylaminoethanol.
$C_9H_{13}NO_2$=167.2
CAS — 59-42-7.
ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.
ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.
UNII — 1WS297W6MV.

NOTE. Synephrine has been used as a synonym for oxedrine (p. 1463.1). Care should be taken to avoid confusion with phenylephrine (*m*-synephrine).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phenylephrine). A white or almost white crystalline powder. Slightly soluble in water and in alcohol; sparingly soluble in methyl alcohol. It dissolves in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Phenylephrine Acid Tartrate

Bitartrato de fenilefrina; Fenilefrina, bitartrato de; Phenylephrine Bitartrate (rINNM); Phényléphrine, Bitartrate de; Phenylephrine Tartrate (BANM); Phenylephrini Bitartras; Tartrato ácido de fenilefrina; Фенилэфрина битартрат.
$C_9H_{13}NO_2.C_4H_6O_6$=317.3
CAS — 13998-27-1.
ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.
ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.
UNII — 27O3Q5ML57.

Pharmacopoeias. In *US.*

USP 36: (Phenylephrine Bitartrate). A white or almost white powder or colourless crystals. Freely soluble in water; pH of a 10% solution in water is between 3.0 and 4.0. Store in airtight containers. Protect from light.

Phenylephrine Hydrochloride *(BANM, rINNM)*

Fenilefrin Hidroklorür; Fenilefrina, hidrocloruro de; Fenilefrin hidroklorid; Fenilefrino hidrochloridas; Fenylefrin hydrochlorid; Fenylefrinhydroklorid; Fenylefryny chlorowodorek; Fenyyliefriinihydrokloridi; Hidrocloruro de fenilefrina; Mesatonum; Metaoxedrini Chloridum; Phényléphrine, Chlorhydrate de; Phenylephrinhydrochlorid; Phenylephrini Hydrochloridum; Фенилэфрина Гидрохлорид.
$C_9H_{13}NO_2.HCl$=203.7
CAS — 61-76-7.
ATC — C01CA06; R01AA04; R01AB01; R01BA03; S01FB01; S01GA05.
ATC Vet — QC01CA06; QR01AA04; QR01AB01; QR01BA03; QS01FB01; QS01GA05.
UNII — 04JAS9TNSJ.

NOTE. PHNL is a code approved by the BP 2014 for use on single unit doses of eye drops containing phenylephrine hydrochloride where the individual container may be too small to bear all the appropriate labelling information. PHNCYC is a similar code approved for eye drops containing phenylephrine hydrochloride and cyclopentolate hydrochloride.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Phenylephrine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol.

USP 36: (Phenylephrine Hydrochloride). White or practically white, odourless, crystals. Freely soluble in water and in alcohol. Store in airtight containers at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Phenylephrine hydrochloride is a sympathomimetic (p. 1507.3) with mainly direct effects on adrenergic receptors. It has mainly alpha-adrenergic activity and in without significant stimulating effects on the CNS at usual doses. Its pressor activity is weaker than that of noradrenaline (p. 1458.3) but of longer duration. After injection it produces peripheral vasoconstriction and increased arterial pressure; it also causes reflex bradycardia. It reduces blood flow to the skin and to the kidneys.

Phenylephrine and its salts are most commonly used either topically or orally, for the symptomatic relief of nasal **congestion** (but see p. 1673.1). They are frequently included in preparations intended for the relief of cough and cold symptoms. For nasal congestion, a 0.25 to 1% solution may be instilled as nasal drops or a spray into each nostril every 4 hours as required, or phenylephrine hydrochloride may be given in usual oral doses of 10 mg every four hours (up to a maximum of 60 mg daily) or 12 mg up to four times daily.

In ophthalmology, phenylephrine hydrochloride is used as a **mydriatic** (p. 2000.2) in concentrations of up to 10%; generally solutions containing 2.5 or 10% are used but systemic absorption can occur (see Effects on the Cardiovascular System, p. 1673.2) and the 10% strength, in particular, should be used with caution. The mydriatic effect can last several hours. Solutions containing 2.5% or more may cause intense irritation and a local anaesthetic should be instilled into the eye a few minutes beforehand.

Ocular solutions containing lower concentrations (usually 0.12% phenylephrine hydrochloride) are used as a **conjunctival decongestant** (see Conjunctivitis, p. 611.1).

Phenylephrine has been used parenterally in the treatment of hypotensive states, such as those encountered during circulatory failure or spinal anaesthesia. Phenyleph-

rine has also been used in orthostatic hypotension (see under Fludrocortisone, p. 1634.3). For **hypotension**, an initial dose of phenylephrine hydrochloride 2 to 5 mg may be given as a 1% solution subcutaneously or intramuscularly with further doses of 1 to 10 mg if necessary, according to response. A dose of 100 to 500 micrograms by slow intravenous injection as a 0.1% solution, repeated as necessary after at least 15 minutes, has also been used. In severe hypotensive states, 10 mg in 500 mL of glucose 5% or sodium chloride 0.9% has been infused intravenously, initially at a rate of up to 180 micrograms/minute, reduced, according to the response, to 30 to 60 micrograms/minute.

For doses in children, see below.

Phenylephrine hydrochloride has been given by intravenous injection to stop **paroxysmal supraventricular tachycardia** but other drugs are preferred (see Cardiac Arrhythmias, p. 1266.1). The initial dose is usually not greater than 500 micrograms given as a 0.1% solution with subsequent doses gradually increased in increments of 100 to 200 micrograms up to 1 mg if necessary.

Phenylephrine hydrochloride has been used for its vasoconstrictor action as an **adjunct** to local anaesthetics.

Phenylephrine has also been used as the acid tartrate to prolong the bronchodilator effects of isoprenaline when given by inhalation. However, isoprenaline is now little used by this route.

Phenylephrine tannate has also been used.

Administration in children. Phenylephrine hydrochloride is used for the symptomatic relief of **nasal congestion**; however, over-the-counter cough and cold preparations containing sympathomimetic decongestants (including phenylephrine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. In the USA, phenylephrine hydrochloride may be used in children aged from 6 to 12 years; 2 or 3 drops, or 1 or 2 sprays, of a 0.25% solution may be instilled into each nostril every four hours as needed. In the UK, oral preparations for nasal congestion associated with colds and hay fever are not licensed in children under 12 years of age.

Phenylephrine hydrochloride is used for **mydriasis** in diagnostic or therapeutic procedures. Solutions containing 2.5% are used in children as the 10% strength is contra-indicated owing to the risk of systemic effects.

For acute **hypotension**, phenylephrine hydrochloride may be given subcutaneously or intramuscularly; the following doses, according to age, are suggested in the *BNFC*:

- 1 to 12 years: 100 micrograms/kg every 1 to 2 hours as needed (to a maximum dose of 5 mg)
- 12 to 18 years: 2 to 5 mg, followed if necessary by further doses of 1 to 10 mg (maximum initial dose 5 mg)

Although the intravenous route is not licensed in the UK for such use in children, intravenous injection is preferred to the other parenteral routes; the *BNFC* recommends the following doses given as a 0.1% solution:

- 1 to 12 years: 5 to 20 micrograms/kg (maximum 500 micrograms), repeated as needed after at least 15 minutes
- 12 to 18 years: 100 to 500 micrograms, repeated as needed after at least 15 minutes

For intravenous infusion, the solution is diluted with glucose 5% or sodium chloride 0.9% to a concentration of 20 micrograms/mL and given as a continuous infusion via a central venous catheter. The *BNFC* gives the following doses:

- 1 to 16 years: 100 to 500 nanograms/kg per minute, adjusted according to response
- 16 to 18 years: initially up to 180 micrograms/minute, reduced to 30 to 60 micrograms/minute according to response

Faecal incontinence. Topical application of phenylephrine gel has been shown to increase resting anal tone[1] and has been investigated in patients with faecal incontinence.[2] Although application of a 10% gel did not appear to be of clinical benefit in a double-blind crossover study in 36 patients with faecal incontinence caused by internal sphincter dysfunction,[3] continence was improved in another small study in patients with ileoanal pouches.[4]

1. Cheetham MJ, *et al.* Topical phenylephrine increases anal canal resting pressure in patients with faecal incontinence. *Gut* 2001; 48: 356–9.
2. Cheetham MJ, *et al.* Drug treatment for faecal incontinence in adults. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 04/01/07).
3. Carapeti EA, *et al.* Randomized controlled trial of topical phenylephrine in the treatment of faecal incontinence. *Br J Surg* 2000; 87: 38–42.
4. Carapeti EA, *et al.* Randomized, controlled trial of topical phenylephrine for fecal incontinence in patients after ileoanal pouch construction. *Dis Colon Rectum* 2000; 43: 1059–63.

Nasal congestion. A meta-analysis concluded that there was insufficient evidence that phenylephrine 10 mg was an effective oral decongestant (p. 1652.1).[1]

1. Hatton RC, *et al.* Efficacy and safety of oral phenylephrine: systematic review and meta-analysis. *Ann Pharmacother* 2007; 41: 381–90.

Priapism. Alpha agonists, including phenylephrine, may be used in the management of priapism (see under Metaraminol, p. 1430.2). For reference to phenylephrine in low dosage and dilute solution being given by intracavernosal injection to reverse priapism, see under Alprostadil, p. 2353.2.

Adverse Effects and Precautions

As for Sympathomimetics, p. 1508.2 and p. 1508.3; phenylephrine has mainly alpha-agonist effects. It has a longer duration of action than noradrenaline and an excessive vasopressor response may cause a prolonged rise in blood pressure. It induces tachycardia or reflex bradycardia and should therefore be avoided in severe hyperthyroidism and used with caution in severe ischaemic heart disease. Patients with diabetes mellitus or prostatic hyperplasia should also avoid phenylephrine.

Since phenylephrine is absorbed through the mucosa systemic effects may follow application to the eyes or the nasal mucosa. In particular, phenylephrine 10% eye drops can have powerful systemic effects. They should be avoided or only used with extreme caution in infants, the elderly, and in patients with cardiac disease, significant hypertension, or advanced arteriosclerosis. Fatalities have been reported in patients with pre-existing cardiovascular disease.

Use of phenylephrine in the eye may liberate pigment granules from the iris, especially when given in high doses to elderly patients. Ophthalmic solutions of phenylephrine are contra-indicated in patients with angle-closure glaucoma. Corneal clouding may occur if corneal epithelium has been denuded or damaged.

Excessive or prolonged use of phenylephrine nasal drops can lead to rebound congestion.

Phenylephrine hydrochloride is irritant and may cause local discomfort at the site of application; extravasation of the injection may even cause local tissue necrosis.

Effects on the cardiovascular system. Systemic adverse effects have occurred after the use of phenylephrine as eye drops (particularly at a strength of 10%), or nasal drops.

Hypertension[1] and hypertension with pulmonary oedema[2] have been described in infants and children after the use of phenylephrine 10% eye drops. Hypertension with arrhythmias has also been reported in an 8-year-old child[3] and in an adult[4] after phenylephrine 10% eye drops had been used. Details have also been published on a series of 32 patients who had systemic cardiovascular reactions, including fatal myocardial infarctions, after the use of phenylephrine 10% solutions in the eye.[5] Severe cardiovascular adverse reactions have also been reported with the use of phenylephrine as topical 10% ocular[6] or 0.25% nasal[7] pledgets.

Although the incidence of such reactions seems low,[8] the use of lower concentrations[1,5] and caution in susceptible patients such as those with cardiovascular disorders or the elderly,[9] have been advocated. A reduction in the eye-drop volume has been found to produce adequate mydriasis and may reduce systemic absorption and the risk of adverse cardiovascular effects.[9,10]

1. Borromeo-McGrail V, *et al.* Systemic hypertension following ocular administration of 10% phenylephrine in the neonate. *Pediatrics* 1973; 51: 1032–6.
2. Baldwin FJ, Morley AP. Intraoperative pulmonary oedema in a child following systemic absorption of phenylephrine eyedrops. *Br J Anaesth* 2002; 88: 440–2.
3. Vaughan RW. Ventricular arrhythmias after topical vasoconstrictors. *Anesth Analg* 1973; 52: 161–5.
4. Lai Y-K. Adverse effect of intraoperative phenylephrine 10%: case report. *Br J Ophthalmol* 1989; 73: 468–9.
5. Fraunfelder FT, Scafidi AF. Possible adverse effects from topical ocular 10% phenylephrine. *Am J Ophthalmol* 1978; 85: 447–53.
6. Fraunfelder FW, *et al.* Adverse systemic effects from pledgets of topical ocular phenylephrine 10%. *Am J Ophthalmol* 2002; 134: 624–5.
7. Hecker RB, *et al.* Myocardial ischemia and stunning induced by topical intranasal phenylephrine pledgets. *Mil Med* 1997; 162: 832–5.
8. Brown MM, *et al.* Lack of side effects from topically administered 10% phenylephrine eyedrops: a controlled study. *Arch Ophthalmol* 1980; 98: 487–9.
9. Craig EW, Griffiths PG. Effect on mydriasis of modifying the volume of phenylephrine drops. *Br J Ophthalmol* 1991; 75: 222–3.
10. Wheatcroft S, *et al.* Reduction in mydriatic drop size in premature infants. *Br J Ophthalmol* 1993; 77: 364–5.

Effects on the eyes. Acute and chronic conjunctivitis has been reported[1] after use of over-the-counter ophthalmic decongestant preparations of phenylephrine, naphazoline, or tetryzoline. The conjunctival inflammation took several weeks to resolve in some cases. Dermatoconjunctivitis[2] has also been reported after use of phenylephrine eye drops.

1. Soparkar CN, *et al.* Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. *Arch Ophthalmol* 1997; 115: 34–8.
2. Moreno-Ancillo A, *et al.* Allergic contact reactions due to phenylephrine hydrochloride in eyedrops. *Ann Allergy Asthma Immunol* 1997; 78: 569–72.

Effects on mental function. Hallucinations and paranoid delusions have been reported[1] in a patient after excessive use of a nasal spray containing phenylephrine 0.5%. Mania has also followed the use of large oral doses.[2]

1. Snow SS, *et al.* Nasal spray 'addiction' and psychosis: a case report. *Br J Psychiatry* 1980; 136: 297–9.
2. Waters BGH, Lapierre YD. Secondary mania associated with sympathomimetic drug use. *Am J Psychiatry* 1981; 138: 837–40.

Hypersensitivity. Cross-sensitivity to phenylephrine has been reported in a patient hypersensitive to pseudoephedrine.[1] See also Effects on the Eyes, above.

1. Buzo-Sanchez G, *et al.* Stereoisomeric cutaneous hypersensitivity. *Ann Pharmacother* 1997; 31: 1091.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenylephrine for cardiac or ophthalmic use as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. Phenylephrine has mainly direct alpha-agonist properties and is less liable than adrenaline or noradrenaline to induce ventricular fibrillation if used as a pressor agent during anaesthesia with inhalational anaesthetics such as cyclopropane and halothane; nevertheless, caution is necessary. Since phenylephrine is absorbed through the mucosa, interactions may also follow topical application, particularly in patients receiving an MAOI (including a RIMA). See also under Phenelzine (p. 445.1) and Moclobemide (p. 438.1).

Cardiovascular drugs. Hypertensive reactions have been reported in a patient stabilised on *debrisoquine* when given phenylephrine orally,[1] in patients receiving *reserpine* or *guanethidine* when given phenylephrine eye drops,[2] and a fatal reaction occurred in a patient receiving *propranolol* and *hydrochlorothiazide* also after the instillation of phenylephrine eye drops.[3]

1. Aminu J, *et al.* Interaction between debrisoquine and phenylephrine. *Lancet* 1970; ii: 935–6.
2. Kim JM, *et al.* Hypertensive reactions to phenylephrine eyedrops in patients with sympathetic denervation. *Am J Ophthalmol* 1978; 85: 862–8.
3. Cass E, *et al.* Hazards of phenylephrine topical medication in persons taking propranolol. *Can Med Assoc J* 1979; 120: 1261–2.

Pharmacokinetics

Phenylephrine has low oral bioavailability owing to irregular absorption and first-pass metabolism by monoamine oxidase in the gut and liver. When injected subcutaneously or intramuscularly it takes 10 to 15 minutes to act; subcutaneous and intramuscular injections are effective for up to about 1 hour and up to about 2 hours, respectively. Intravenous injections are effective for about 20 minutes.

Systemic absorption follows topical application.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fadalefrina; Poen Efrina; Prefrin; Qura Nasal; *Austral.*: Actifed PE†; Albalon Relief; Codral Relief Decongestant; Dimetapp PE Nasal Decongestant; Neo-Synephrine; Nyal Cold + Flu; Nyal Decongestant; Nyal Nasal Decongestant PE; Nyal Sinus Relief PE; Prefrin; Sudafed PE; *Austria*: Visadron; *Belg.*: Spraydil; Visadron; *Braz.*: Denason; *Canad.*: Ak-Dilate; Dionephrine; Hemorrhoidal Relief; Little Noses Decongestant; Mydfrin; Neo-Synephrine; Prefrin†; Sudafed PE; Triaminic Thin Strips Nasal Congestion; *Chile*: Mydfrin; *China*: Wei Li Ang (维力昂); *Cz.*: Humex Nosni; Neo-Synephrine; *Fin.*: Oftan Metaoksedrin; *Fr.*: Humoxal; *Ger.*: Neosynephrin-POS; Otriven Baby†; Visadron; *Gr.*: Ibition; Prefrin; *Hong Kong*: Mydfrin; Prefrin†; Visopt†; *India*: Drosyn; Fencel; Frenin; Lefrine; Nefrisol; *Israel*: Efrin; Neo-Synephrine†; *Ital.*: Isonefrine; Nasomixin CM; Neo-Synephrine; *Malaysia*: Mydfrin; Prefrin; *Mex.*: Actifed Advance; Dilufrin†; Lefrine†; Nefrin; Plegh; Rinolan; *Mon.*: Neosynephrine; *Neth.*: Boradrine†; Visadron; *NZ*: Albalon Relief; Neosynephrine; Prefrin; Sudafed PE Nasal Decongestant; *Philipp.*: Decolgen†; Mydfrin; Neo-Synephrine; *Pol.*: Neosynephrin; *Port.*: Davinefrina; Neo-Sinefrina; VibrocilFen; Visadron; *Rus.*: Irifrin (Ирифрин); Mesaton (Мезатон); Nazol Baby (Назол Беби); Nazol Kids (Назол Кидс); Rhinopront (Ринопронт); *S.Afr.*: I-Glo; Naphensyl; Prefrin; *Singapore*: Mydfrin†; Prefrin; *Spain*: ADA†; Boraline†; Disneumon Mentol†; Disneumon Pernasal; Mirazul; Visadron; Vistafrin†; *Switz.*: Neo-Synephrine; Rexophtal N†; Spray nasal pour enfants†; *Turk.*: Mydfrin; *UK*: Boots Decongestant Capsules; Fenox; Non-Drowsy Sudafed Congestion Relief; *Ukr.*: Glycodin (Гликодин)†; Nasol Baby (Назол Беби); *USA*: AH-chew D; Ak-Dilate; Anu-Med; Children's Nostril; Hemorrhoidal Suppositories; Lusonal; Mydfrin; Nasop†; Neo-Synephrine; Neofrin; Nostril; Ocu-Phrin; Pedia Care Childrens Decongestant; Phenyl-T†; Rectacaine; Relief†; Rhinall;

Sinex; Sudafed PE; Triaminic Infant Thin Strips Decongestant†; Triaminic Thin Strips Cold; Tronolane.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in: *Braz.*: Anestesico.

Pharmacopoeial Preparations
BP 2014: Phenylephrine Eye Drops; Phenylephrine Injection; **USP 36:** Antipyrine, Benzocaine, and Phenylephrine Hydrochloride Otic Solution; Isoproterenol Hydrochloride and Phenylephrine Bitartrate Inhalation Aerosol; Phenylephrine Hydrochloride Injection; Phenylephrine Hydrochloride Nasal Jelly; Phenylephrine Hydrochloride Nasal Solution; Phenylephrine Hydrochloride Ophthalmic Solution.

Phenylpropanolamine *(BAN, rINN)*

Fenilpropanolamina; Fenylpropanolamin; Fenyylipropanoliamiini; Phénylpropanolamine; Phenylpropanolaminum; Фенилпропаноламин; (±)-Norephedrine.

(*1RS,2SR*)-2-Amino-1-phenylpropan-1-ol.

$C_9H_{13}NO$=151.2

CAS — 14838-15-4.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

UNII — 33RU150WUN.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of phenylpropanolamine:

Pseudocaine.

Phenylpropanolamine Hydrochloride

(BANM, rINNM)

Fenilpropanolamina, hidrocloruro de; Fenilpropanolaminhidroklorid; Fenilpropanolamino hidrochloridas; Fenylpropanolamin hydrochlorid; Fenylpropanolaminhydroklorid; Fenyylipropanoliamiinihydrokloridi; Hidrocloruro de fenilpropanolamina; Mydriatin; Phénylpropanolamine, Chlorhydrate de; Phenylpropanolaminhydrochlorid; Phenylpropanolamini Hydrochloridum; Фенилпропаноламина Гидрохлорид.

$C_9H_{13}NO,HCl$=187.7

CAS — 154-41-6.

ATC — R01BA01.

ATC Vet — QG04BX91; QR01BA01.

UNII — 8D5I63UE1Q.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

US also includes phenylpropanolamine bitartrate.

Ph. Eur. 8: (Phenylpropanolamine Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water and in alcohol; practically insoluble in dichloromethane.

USP 36: (Phenylpropanolamine Hydrochloride). A white crystalline powder, having a slight aromatic odour. Soluble 1 in 1.1 of water, 1 in 7.4 of alcohol, and 1 in 4100 of chloroform; insoluble in ether. pH of a 3% solution in water is between 4.2 and 5.5. Store in airtight containers. Protect from light.

Uses and Administration

Phenylpropanolamine is a mainly indirect-acting sympathomimetic (p. 1507.3) with an action similar to that of ephedrine (p. 1663.2) but less active as a CNS stimulant.

Phenylpropanolamine has been given orally as the hydrochloride for the symptomatic treatment of **nasal congestion** (p. 1652.1). It has frequently been used in combination preparations for the relief of cough and cold symptoms.

In the management of nasal congestion, phenylpropanolamine hydrochloride has been given in oral doses of up to 50 mg twice daily as modified-release preparations.

Other uses of phenylpropanolamine have included the control of urinary incontinence in some patients and the management of some forms of priapism. Phenylpropanolamine has been used to suppress appetite in the management of obesity but the use of stimulants is no longer recommended.

Phenylpropanolamine polistirex (a phenylpropanolamine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as have phenylpropanolamine bitartrate, phenylpropanolamine maleate, and phenylpropanolamine sulfate.

Adverse Effects and Precautions

As for Ephedrine, p. 1663.3 and p. 1664.1.

Severe hypertensive episodes have followed phenylpropanolamine ingestion (see below). As with other indirect-acting sympathomimetics, tolerance to the therapeutic effects of phenylpropanolamine has been reported with prolonged use.

An extensive and detailed review[1] of adverse effects attributed to phenylpropanolamine noted in 1990 that many of the adverse drug reactions reported in Europe described an alteration of mental status whereas those in North America were more often compatible with hypertension. The author suggested that this might be due to a difference in the isomers present in phenylpropanolamine preparations, based on earlier reports that *d*-norpseudoephedrine, the most potent of several isomeric forms as a stimulant of the CNS, was present in European preparations of phenylpropanolamine. However, later investigation suggests that currently the racemic mixture (±)-norephedrine (*d,l*-norephedrine) is the isomeric form present in commercial preparations in both Europe and the USA.[2]

The original review[1] concentrated on North American cases. The majority of products available were decongestants or cough or cold remedies; a small number were promoted as diet aids.

The data suggested that over-the-counter (OTC) products were more likely to be associated with an adverse reaction than a prescription medication; this may be because such OTC products were more likely to be overused and to be considered innocuous by the patient. It was also likely that drug interactions (below) rather than 'true overdosages' were involved in many of the adverse events, particularly as many OTC preparations contain other ingredients. (See also Abuse under Ephedrine, p. 1664.1, for further discussion about the consequences of use of OTC preparations containing sympathomimetics, including phenylpropanolamine.)

The adverse reactions varied widely ranging from headache and elevated blood pressure to cardiopulmonary arrest, intracranial haemorrhage, and death. Mild reactions included blurred vision, dizziness, anxiety, agitation, tremor, confusion, and hypersensitivity reaction. Severe reactions included hypertensive crisis with hypertensive encephalopathy, seizures, arrhythmias, psychosis, and acute tubular necrosis. One unifying theme of many of the severe cases was that high blood pressure or symptoms suggestive of this were the presenting feature; an acute, persistent, severe headache was also noted in many cases.

It was pointed out that overall phenylpropanolamine was relatively safe. Although billions of doses were consumed annually, few cases of adverse drug reactions had been reported.

It was believed that certain groups may be at particular risk of adverse reactions to phenylpropanolamine: persons with elevated blood pressure, overweight persons (who are likely to be both hypertensive and to use diet aids), patients with eating disorders (who tend to abuse substances including diet aids), and the elderly (who may be multiple drug takers and likely to be hypertensive and at risk already of a stroke).

Subsequently, after a large case-control study in the USA which found an increased risk of haemorrhagic stroke associated with the use of preparations containing phenylpropanolamine (and in particular in women who used phenylpropanolamine as an appetite suppressant),[3] the FDA took steps to remove phenylpropanolamine from all drug products in the USA and requested that it no longer be marketed. Products containing phenylpropanolamine have also been withdrawn in some other countries. However, this study and the FDA decision have been criticised[4-6] notably on the basis that there was no evidence of an increased risk with the amount of phenylpropanolamine normally present in decongestant preparations and the study may have been subject to confounding. The UK CSM[7] considered that the evidence of a link between UK products containing phenylpropanolamine and haemorrhagic stroke was weak (phenylpropanolamine is not licensed as an appetite suppressant in the UK and the maximum recommended dose of 100 mg daily was lower than the 150 mg daily recommended in the USA). It was therefore suggested by UK commentators that use of licensed doses, with appropriate precautions, posed no additional risk.[2] However, subsequently, UK preparations containing phenylpropanolamine have either been reformulated (mainly with pseudoephedrine) or withdrawn by the manufacturers.

1. Lake CR, *et al.* Adverse drug effects attributed to phenylpropanolamine: a review of 142 case reports. *Am J Med* 1990; **89:** 195–208.
2. Moffatt T, *et al.* Phenylpropanolamine: putting the record straight. *Pharm J* 2000; **265:** 817.
3. Kernan WN, *et al.* Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med* 2000; **343:** 1826–32.
4. Ernst ME, Hartz A. Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094.
5. Wolowich WR, *et al.* Phenylpropanolamine and hemorrhagic stroke. *N Engl J Med* 2001; **344:** 1094–5.
6. Stier BG, Hennekens CH. Phenylpropanolamine and hemorrhagic stroke in the Hemorrhagic Stroke Project: a reappraisal in the context of science, the Food and Drug Administration, and the law. *Ann Epidemiol* 2006; **16:** 49–52.
7. CSM/MCA. Phenylpropanolamine and haemorrhagic stroke. *Current Problems* 2001; **27:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007458&RevisionSelectionMethod=LatestReleased (accessed 04/01/07)

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies phenylpropanolamine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 19/10/11)

Interactions

As for Sympathomimetics, p. 1508.3. For a comment that drug interactions were likely to have been involved in many adverse events associated with phenylpropanolamine see under Adverse Effects and Precautions, above. Due to its indirect action, hypertensive crisis is a particular risk in patients receiving MAOIs. For mention of the potential that phenylpropanolamine can increase plasma-caffeine concentrations, see Sympathomimetics, under Caffeine, p. 1206.2.

Amantadine. Severe psychosis has been reported[1] in a woman taking amantadine with phenylpropanolamine. In another report,[2] a 39-year-old man had intense and recurrent *déjà vu* experiences after taking amantadine with phenylpropanolamine for viral influenza. The effect ceased when he stopped both drugs. The authors suggested that his symptoms were due to increased dopamine activity caused by the combination.

1. Stroe AE, *et al.* Psychotic episode related to phenylpropanolamine and amantadine in a healthy female. *Gen Hosp Psychiatry* 1995; **17:** 457–8.
2. Taiminen T, Jääskeläinen SK. Intense and recurrent déjà vu experiences related to amantadine and phenylpropanolamine in a healthy male. *J Clin Neurosci* 2001; **8:** 460–2.

Antipsychotics. A 27-year-old woman with schizophrenia and T-wave abnormality of the heart, who had responded to *thioridazine* 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with phenylpropanolamine hydrochloride 50 mg (*Contac C*), concurrently with thioridazine.[1]

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Antivirals. A patient taking an over-the-counter nasal decongestant preparation containing phenylpropanolamine and clemastine as well as a triple-drug HIV prophylactic regimen, had a hypertensive crisis 3 days after *stavudine* was substituted for *zidovudine*;[1] the other antivirals in the regimen were *indinavir* and *lamivudine*.

1. Khurana V, *et al.* Hypertensive crisis secondary to phenylpropanolamine interacting with triple-drug therapy for HIV prophylaxis. *Am J Med* 1999; **106:** 118–19.

Bromocriptine. For a report of hypertension and life-threatening complications after use of phenylpropanolamine with bromocriptine, see Sympathomimetics, p. 899.1.

NSAIDs. A 27-year-old woman who had been taking D-phenylpropanolamine [sic] 85 mg daily for some months, had severe hypertension when she also took *indometacin* 25 mg. It was considered that the inhibition of prostaglandin synthesis by indometacin might have caused enhancement of the sympathomimetic effect of phenylpropanolamine.[1]

1. Lee KY, *et al.* Severe hypertension after ingestion of an appetite suppressant (phenylpropanolamine) with indomethacin. *Lancet* 1979; **i:** 1110–11.

Pharmacokinetics

Phenylpropanolamine is readily and completely absorbed from the gastrointestinal tract and peak plasma concentrations occur about 1 or 2 hours after oral doses. It undergoes some metabolism in the liver, to an active hydroxylated metabolite, but up to 80 to 90% of a dose is excreted unchanged in the urine within 24 hours. The half-life has been reported to be about 3 to 5 hours.

References.

1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; **129:** 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; **57:** 62–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fin.*: Rinexin; *Ger.*: Boxogetten S; Recatol mono; *Norw.*: Rinexin; *Philipp.*: Desotap†; Disudrin; Naldec; Nasadec; Nasaphen†; Nasathera P; Neo-Coldan; *Swed.*: Rinexin.

Multi-ingredient Preparations. *Chile*: Contac†; Matinor; Sinutab; *Fin.*: Rinomar; *Ger.*: Antiadipositum; Basoplex; Wick Daymed Erkaltungs; *Gr.*: Dimetapp New; Dimetapp; Ornade-2; Rhino-

pront-S; *Hong Kong*: Antamin†; Anticol†; B.P.P.†; BPP Cough Syrup†; Brom-PP; Brom-Ramine Compound; Corhisdin with codeine†; Coritussal†; CPP†; DM-Cordyl†; Eascold; Eurotapp; Fludane†; Neozep; Pholix†; Qualizep; Rhinopront†; Syncold-tab-M†; Tripe P; Tuseran; Uni-Vasin; Vidatapp†; *India*: A-Cof; Abcof-DM; Aceper; Actifed DM; Actifed Plus; Actiflu Plus; Actiflu; Actioner-DX; Alerid Cold; Alerid D; Alernyl-DC; Allset; Altec Cough Formula; Altec-P; Ambrodex; Ambrodil Plus; Ambrol-GPC; Ascoril-D; Asisneez; Bactpar Plus; Biorex; Brick; Brick; Broncare; Broncos; Brontac-Plus; C-Cold; Calmcold; Caimcold; Calscot; Calscot; Capex-DMR; Carecof Exp; Carecof; CC Cap; CC-Koff; CCGO; Celar; Cetcip Cold; Cetcip-D; Cetin Cold; Cetin Kid; Cetin-D; Cetra; Cezcold; Chericold; Cheston Cold; Cheston DT; Cheston; Cindexa; Ciz Cold; Cledex; Cobury-DX; Codril-P; Cof QD; Cofal-D; Cofar-D; Cofdex Forte; Cofdex Forte; Cofdex-P; Cofdex; Cogof; Cold-CZ; Cold-Relief; Cold-War; Coldact Plus; Coldact; Coldant; Coldap; Coldargic; Coldastat-LX; Coldastat; Coldastat; Coldcure; Coldec; Coldfin; Coldgone; Coldilak; Coldoff; Coldtaur; Coldtaur; Coldwar; Coldy; Coldy; Colgin; Colrex Plus; Colsan; Contac-CC; Control; Contus Plus; Contus-650; Contus; Contus; Cor-4; Corophen-D; Cos-D; Coscopin-BR; Cosome Exp; Cosome; Covil-A; Cozy Cool; CPP; Cuf-Dex; Cufcalm; Cuffmol-P; Cufree; CZ-Cold; DCol-BR; Decold CP; Decomine; Delcon Plus; Delcon; Demine; Dencold; Dex-PC; Dexcof; Dexphen; Dextrotuss; Dolar; Dold; Dolo-Cold; DPC; Drynoz; DSQ; Dual Cold; Easicold; Elcold; Elgnil Cold; Ephact-XR; Ephedrex; Eskold Expectorant; Eskold; Est-Coff; Etric Plus; Evercold; Fenace Plus; Fevacold; Fincof; Fineorest; Flemnil; Flu-4-DMR; Flucold; Flucold; Flukuff; Fluzet; Fricold; Fricold; Grillinctus†; Idalez Plus; Ifycet; Incold; Incold; Incough-DX; Kaituss; Kazibrox; Kofrid-D; Kofryl-P; Koftane; Kol-DC; Kolderon; Kozifed; Kuff-D; Kuff-Q; Kuffdac-C; Kufgen-D; Kufkair-P; L-Cit Plus; L-Triz Plus; LCZ-Plus; Leday-CC; Lemohist-C; Lemohist; Lemohist; Lenex; Lenomol; Leverest Plus; Levogo Plus; Levoriz Plus; Levostar Plus; Levostar-D; Lexcof; LG-Plus; Libitus; Lincotuss-P; Linctus-DX; Littlekof-DM; Lorex-AP; Lucold; Marcold; Nicip Cold; Nocold; Nocold; Rinostat; Zeet Linctus; Zeet; *Indon.*: Agrippin†; Allerin; Alpara; Anacetine; Anadex; Antiza; Benilin†; Bestocol; Bodrexin; Bronchophen†; Calorex†; Codecon; Colfin; Collerin Expectorant; Colza†; Combi Flu; Corsagrip; Cosyr†; Cough EN Expectorant; Cough EN Plus; Decolgen; Decolgen; Decolsin; Deconal; Dextral; Dextrosin Anak; Dextrosin; Extra-Flu; Farapon; Flu Stop; Flu-Tab; Flucadex†; Flucodin; Flucyl†; Fludane Plus; Fludane; Flunadin†; Flunax†; Flutamol-P; Flutamol; Fluzep; Fortaflu†; Frigrip; Gunacold†; Intunal; Kontrabat; Lacoldin; Lapisiv; Mixaflu; Mixagrip; Molexflu; Mucotussan†; Nalgestan; Neo Novapon Plus; Neo Novapon; Neozep; New Coldin†; Nodrof; Oskadon Flu & Batuk Berdahak; Paranomin; Paratusin; Pilexal; Ponflu; Protusif†; Pyridryl Plus; Recomint; Sanaflu Plus; Sanaflu; Stop Cold; Topras; Triadex; Tuseran Forte†; Tuseran†; Tuzalos; Ultragrip†; Ultragrip; *Irl.*: Day & Night†; *Mex.*: Graneodin D Mentol; Lentostamin†; Numonyl Jarabe†; *Philipp.*: A-P-Histallin†; AC Nex; Allerin Reformulated; Coldrex Reformulated†; Colvan; Colvan; Congestril (Reformulated); Conotab; Cynosal; Decolsin Reformulated; Drinus; Drinus; Dynatussin; Dynatussin; Eleobron; Hisdec Mucobron Forte; Mucotuss; Myracof-AF†; Myracof-T†; Nafarin A (Reformulated); Nagelin; Nasagesic; Nasatapp; Nasathera CPM; Nasathera; Neo-Bromexan Forte; Neo-Bromexan; Nosteror†; Noxifen; Omex; Pediatapp; Penbrosol; Piemerid†; PPB; Rhinodec; Rhinotapp; Sinutab Extra Strength; Solvamin; Tridecon; Tuseran (Reformulated)†; Zeditapp; *S.Afr.*: Adco-Sinal Co; Betalix†; Colcaps†; Coldvico†; Eskomade†; Flustat†; Infacet†; Merck-Flu†; Nitecall†; Ornacol†; Rinex†; Si-Nade†; Sinuclear; Sinustat Flu†; Sinustat; Sinustop with Codeine†; Sinustop†; Sinutab ND; Sinutab with Codeine; Sinutab†; *Spain*: Irritos†; Senioral; *Swed.*: Rinomar; *Thai.*: Aorinyl; Clinepect; *Turk.*: Alfarol; Apex; Cetaflu-forte; Contex; Corsal; Ekorinol†; Parol Cold; Rhinopront; Rhinotussal; *Ukr.*: Flucoldex (Флюколдекс).

Pharmacopoeial Preparations

USP 36: Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Capsules; Phenylpropanolamine Hydrochloride Extended-release Capsules; Phenylpropanolamine Hydrochloride Extended-release Tablets; Phenylpropanolamine Hydrochloride Oral Solution; Phenylpropanolamine Hydrochloride Tablets.

Pholcodine *(BAN, rINN)*

Folcodina; Folkodiini; Folkodin; Folkodin monohydrát; Folkodinas; Pholcodin; Pholcodinum; Pholcodinum Monohydricum; Фолкодин.

3-*O*-(2-Morpholinoethyl)morphine monohydrate.

$C_{23}H_{30}N_2O_4,H_2O$=416.5

CAS — 509-67-1 (anhydrous pholcodine).

ATC — R05DA08.

ATC Vet — QR05DA08.

UNII — LPP64AWZ7L.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii).

Ph. Eur. 8: (Pholcodine). A white or almost white crystalline powder or colourless crystals. Sparingly soluble in water; freely soluble in alcohol and in acetone; dissolves in dilute mineral acids.

Uses and Administration

Pholcodine is a centrally acting cough suppressant that has actions and uses similar to those of dextromethorphan (p. 1660.2). It is given orally in a usual dose of 5 to 10 mg three or four times daily. For doses in children, see below. The citrate has also been used. Pholcodine polistirex (a pholcodine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has been used in modified-release preparations.

Administration in children. Although pholcodine is licensed for use in children, over-the-counter cough and cold preparations containing cough suppressants (including pholcodine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. The *BNFC* suggests giving those aged 6 to 12 years 2 to 5 mg three or four times daily.

Adverse Effects and Precautions

As for Dextromethorphan, p. 1660.3. Constipation, drowsiness, and skin rashes have been reported occasionally.

Support for a hypothesis that consumption of pholcodine may sensitise individuals to hypersensitivity to neuromuscular blockers has resulted in one pholcodine preparation being taken off the Norwegian market in March 2007.[1] A subsequent retrospective analysis in Sweden, where pholcodine had not been available since mid 1989, of serum samples taken from patients who had had IgE-mediated allergy appeared to support this hypothesis.[2]

1. Florvaag E, Johansson SGO. The pholcodine story. *Immunol Allergy Clin North Am* 2009; 29: 419–27.
2. Johansson SGO, *et al.* Pholcodine caused anaphylaxis in Sweden 30 years ago. *Allergy* 2009; 64: 820–1.

Interactions

Use of pholcodine with alcohol or other CNS depressants may increase the effects on the CNS.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Actifed CC Dry†; Chemists Own Dry Cough; Duro-Tuss Dry Cough; Tussinol†; *Belg.*: Cotrane Pholcodine; *China*: Pholcotussin (欧博士福尔可定); *Fin.*: Tuxit†; *Fr.*: Atouxx Toux Seche†; Biocalyptol; Dimetane; Flucalyptol; Humex Toux Seche Pholcodine†; Pharmakod toux seche†; Respilene†; Rhinathiol Toux Seche Pholcodine†; Valda Toux Seche†; *Hong Kong*: Duro-Tuss; Uni-Pholco; *Irl.*: Expulin Dry Cough†; Pholcodex; Pholcolin†; *Malaysia*: Dhacodine; Ducodin; Duro-Tuss; *NZ*: Benadryl Dry Tickly Cough; Duro-Tuss Dry Cough; *S.Afr.*: Pholcolinct†; Pholtex; *Singapore*: Duro-Tuss; *UK*: Benylin Childrens Dry Coughs; Boots Dry Cough Syrup 1 Year Plus; Galenphol; Hill's Balsam Dry Cough; Pavacol-D; Tixylix Dry Cough†.

Multi-ingredient Preparations. *Austral.*: Chemists Own Kiddicol; Demazin Cough & Cold†; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Duro-Tuss Decongestant†; Duro-Tuss Dry Cough Plus Nasal Decongestant; Duro-Tuss Dry Cough; Duro-Tuss Expectorant; Duro-Tuss PE Dry Cough plus Nasal Decongestant; Tixylix Night†; *Belg.*: Broncho-pectoralis Pholcodine; Eucalyptine Pholcodine; Pholco-Mereprine; *China*: Ao Si Ling (奥斯灵); Photifed-M (澳特斯); *Fr.*: Atouxx†; Broncalene; Clarix Toux Seche†; Hexapneumine†; Hexapneumine; Pholcodyl†; Polery; Pulmosodyl; Trophires†; *Hong Kong*: Double 'P' Syrup†; Duro-Tuss Decongestant; Duro-Tuss Expectorant; Hexapneumine; Pholix†; Tripe P; *India*: Childryl; Lincotuss-P; Tixylix; *Irl.*: Day Nurse; Expulin Childrens Cough†; Expulin†; Nirolex Day Cold & Flu; Solpadeine Cold & Flu; *Malaysia*: Difflam Anti-Inflammatory Lozenges (with cough suppressant); Duro-Tuss Expectorant; Phensedyl Dry Cough; Promedyl Plus; Rhynacol†; Russedyl Plus; *NZ*: Difflam Cough; Duro-Tuss Cough†; Duro-Tuss Expectorant; Duro-Tuss Lozenges; Tixylix; *S.Afr.*: Contra-Coff†; Docsed†; Folcofen; Pholtex Linctus; Procof; Respinol Compound†; Tixylix†; *Singapore*: Difflam Cough Lozenges; Duro-Tuss Cough Lozenges; Duro-Tuss Decongestant†; Duro-Tuss Expectorant; *Spain*: Caltoson Balsamico†; *Switz.*: Pecto-Baby†; Phol-Tussil; Phol-Tux; *UK*: Boots Nightime Cough Syrup 1 Year Plus; Cough Nurse; Day & Night Nurse; Day Nurse; Nirolex Day Cold & Flu; Nirolex Night Cold & Flu; Tixylix Cough & Cold†; Tixylix Night-Time†; *Ukr.*: Hexapneumine for Children (Гексапневмин Для Детей)†.

Pharmacopoeial Preparations

BP 2014: Pholcodine Linctus; Strong Pholcodine Linctus.

Pipazetate *(BAN, rINN)*

D-254; Pipazetate; Pipazetato; Pipazetatum; Pipazethate (USAN); SKF-70230-A; SQ-15874; Пипазетат.

2-[2-Piperidinoethoxy]ethyl pyrido[3,2-*b*][1,4]benzothiazine-10-carboxylate.

$C_{21}H_{25}N_3O_3S$=399.5

CAS — 2167-85-3.

ATC — R05DB11.

ATC Vet — QR05DB11.

UNII — M5EK1T5V2L.

Pipazetate Hydrochloride *(BANM, rINNM)*

Hidrocloruro de pipazetato; Pipazétate, Chlorhydrate de; Pipazetati Hydrochloridum; Pipazetato, hidrocloruro de; Pipazethate Hydrochloride; Piperestazine Hydrochloride; Пипазетата Гидрохлорид.

$C_{21}H_{25}N_3O_3S,HCl$=436.0

CAS — 6056-11-7.

ATC — R05DB11.

ATC Vet — QR05DB11.

UNII — 757GN3W2CZ.

Profile

Pipazetate hydrochloride is a centrally acting cough suppressant that also has some peripheral actions in non-productive cough. It has been given orally and rectally.

Overdosage. A healthy 4-year-old child became somnolent and agitated, with convulsions, followed by coma, after swallowing an unknown number of tablets containing pipazetate; cardiac arrhythmias also developed.[1] Fatal toxicity has also been reported in children.[2,3]

1. da Silva OA, Lopez M. Pipazethate—acute childhood poisoning. *Clin Toxicol* 1977; 11: 455–8.
2. Bonavita V, *et al.* Accidental lethal pipazethate poisoning in a child. *Z Rechtsmed* 1982; 89: 145–8.
3. Soto E, *et al.* Pipazethate lethality in a baby. *Vet Hum Toxicol* 1993; 35: 41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Selvigon; *Gr.*: Selvigon; *Indon.*: Selvigon; *Ital.*: Selvigon; *Mex.*: Selvigon.

Multi-ingredient Preparations. *Indon.*: Transpulmin.

Poppy Capsule

Dormideiras; Fruit du Pavot; Fruto de adormidera; Mohnfrucht; Papaveris Capsula; Poppy Heads; Маковая Коробочка.

Pharmacopoeias. In *Chin.*

Profile

Poppy capsule consists of dried fruits of *Papaver somniferum* (Papaveraceae), collected before dehiscence has occurred, containing very small amounts of morphine with traces of other opium alkaloids. It is mildly sedative and has been used as a liquid extract or syrup in cough mixtures.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Sedemol; Sulfa-Sedemol; *Braz.*: Malvodon†; *Fr.*: Mediflor Pectorale d'Alsace no 8†.

Prenoxdiazine Hydrochloride *(rINNM)*

Hidrocloruro de prenoxdiazina; HK-256; Prenoxdiazin Hydrochloride; Prenoxdiazina, hidrocloruro de; Prénoxdiazine, Chlorhydrate de; Prenoxdiazini Hydrochloridum; Преноксдиазина Гидрохлорид.

3-(2,2-Diphenylethyl)-5-(2-piperidinoethyl)-1,2,4-oxadiazole hydrochloride.

$C_{23}H_{27}N_3O,HCl$=397.9

CAS — 47543-65-7 (prenoxdiazine); 37671-82-2 (prenoxdiazine hibenzate); 982-43-4 (prenoxdiazine hydrochloride).

ATC — R05DB18.

ATC Vet — QR05DB18.

Profile

Prenoxdiazine hydrochloride is a peripherally acting cough suppressant for non-productive cough that has been given orally. Prenoxdiazine hibenzate has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hung.*: Libexin; Rhinathiol Tusso; *India*: Libexin; *Rus.*: Libexin (Либексин); *Ukr.*: Libexin (Либексин).

Multi-ingredient Preparations. *Ital.*: Libexin Mucolitico.

Promolate *(rINN)*

Morphethylbutyne; Promolato; Promolatum; Промолат.
2-Morpholinoethyl 2-methyl-2-phenoxypropionate.
$C_{16}H_{23}NO_4$=293.4
CAS — 3615-74-5.
UNII — 5WGM277OKR.

Profile

Promolate is a cough suppressant that has been given rectally to infants.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Atusil.

Pseudoephedrine *(BAN, rINN)* ⊗

d-Isoephedrine; Pseudoefedriini; Pseudoefedrin; Pseudoefedrina; Pseudoéphédrine; Pseudoephedrinum; *d*-Ψ-Ephedrine; Псевдоэфедрин.
(+)-(1*S*,2*S*)-2-Methylamino-1-phenylpropan-1-ol.
$C_{10}H_{15}NO$=165.2
CAS — 90-82-4.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — 7CUC9DDI9F.

Description. Pseudoephedrine is an alkaloid obtained from *Ephedra* spp.

Pseudoephedrine Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de pseudoefedrina; Pseudoefedriinihydrokloridi; Pseudoefedrina, hidrocloruro de; Pseudoefedrin-hydrochlorid; Pseudoefedrinhydroklorid; Pseudoefedrino hidrochloridas; Pseudoéphédrine, Chlorhydrate de; Pseudoephedrinhydrochlorid; Pseudoephedrini hydrochloridum; Pseudoefedrin Hidroklorür; Pszeudoefedrin-hidroklorid; Псевдоэфедрина Гидрохлорид.
$C_{10}H_{15}NO.HCl$=201.7
CAS — 345-78-8.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — 6V9V2RYJ8N.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Pseudoephedrine Hydrochloride). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water and in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Pseudoephedrine Hydrochloride). A fine, white to off-white crystalline powder, having a faint characteristic odour. Soluble 1 in 0.5 of water, 1 in 3.6 of alcohol, 1 in 91 of chloroform, and 1 in 7000 of ether. pH of a 5% solution in water is between 4.6 and 6.0. Store in airtight containers. Protect from light.

Pseudoephedrine Sulfate

(BANM, USAN, rINNM) ⊗

Pseudoefedrina, sulfato de; Pseudoéphédrine, Sulfate de; Pseudoephedrine Sulphate; Pseudoephedrini Sulfas; Sch-4855; Sulfato de pseudoefedrina; Псевдоэфедрина Сульфат.
$(C_{10}H_{15}NO)_2.H_2SO_4$=428.5
CAS — 7460-12-0.
ATC — R01BA02.
ATC Vet — QR01BA02.
UNII — Y9DL7OPE68.

Pharmacopoeias. In *US*.

USP 36: (Pseudoephedrine Sulfate). Odourless, white crystals or crystalline powder. Freely soluble in alcohol. pH of a 5% solution in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Uses and Administration

Pseudoephedrine is a direct- and indirect-acting sympathomimetic (p. 1507.3). It is a stereoisomer of ephedrine (p. 1663.1) and has a similar action, but has been stated to have less pressor activity and fewer CNS effects.

Pseudoephedrine and its salts are given orally for the symptomatic relief of nasal congestion (p. 1652.1). They are commonly combined with other ingredients in preparations intended for the relief of cough and cold symptoms.

Pseudoephedrine hydrochloride or sulfate are generally given orally in doses of 60 mg every 4 to 6 hours up to a maximum of 4 doses in 24 hours. For doses in children, see below. Modified-release preparations are also available; a usual adult dose is 120 mg every 12 hours or 240 mg every 24 hours.

Other uses of pseudoephedrine include the control of urinary incontinence in some patients and the management of some forms of priapism.

Pseudoephedrine polistirex (a pseudoephedrine and sulfonated diethenylbenzene-ethenylbenzene copolymer complex) has also been used, as has pseudoephedrine tannate.

Administration in children. The *BNFC* states there is little evidence to support the use of systemic decongestants in children. However, a suggested oral dose of pseudoephedrine hydrochloride for the management of mucosal congestion of the upper respiratory tract in those aged 6 to 12 years is 30 mg 3 or 4 times daily.

Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including pseudoephedrine) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2.

Barotrauma. Results from a controlled study[1] suggest that pseudoephedrine given to adults at least 30 minutes before flying appears to decrease the incidence of ear pain associated with pressure changes.[1] However, a similar decrease in risk was not noted in children.[2]

1. Jones JS, *et al.* A double-blind comparison between oral pseudoephedrine and topical oxymetazoline in the prevention of barotrauma during air travel. *Am J Emerg Med* 1998; 16: 262–4.
2. Buchanan BJ, *et al.* Pseudoephedrine and air travel-associated ear pain in children. *Arch Pediatr Adolesc Med* 1999; 153: 466–8.

Adverse Effects and Precautions

As for Ephedrine, p. 1663.3 and p. 1664.1. The commonest adverse effects of pseudoephedrine include tachycardia, anxiety, restlessness, and insomnia; skin rashes and urinary retention have occasionally occurred. Hallucinations have been reported rarely, particularly in children.

Abuse. Acute psychosis and visual and tactile hallucinations have been reported[1] in an 18-year-old male after intravenous misuse of pseudoephedrine hydrochloride. Pseudoephedrine has also been used for the illicit manufacture of street stimulants such as metamfetamine (p. 2324.2).

For reference to toxic effects after long-term use of over-the-counter preparations containing sympathomimetics, such as pseudoephedrine, see under Ephedrine, p. 1664.1.

1. Sullivan G. Acute psychosis following intravenous abuse of pseudoephedrine: a case report. *J Psychopharmacol* 1996; 10: 324–5.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, preparations used by breast-feeding mothers that contain pseudoephedrine with dexbrompheniramine maleate have resulted in crying, irritability, and poor sleep patterns in the infant.

The concentrations of pseudoephedrine and triprolidine in plasma and breast milk of 3 mothers for up to 48 hours after ingestion of a preparation containing pseudoephedrine hydrochloride 60 mg with triprolidine hydrochloride 2.5 mg have been studied.[2] Concentrations of pseudoephedrine in milk were consistently higher than in plasma; the half-life in both fluids was between 4.2 and 7.0 hours. Assuming a generous milk secretion of 500 mL over 12 hours it was calculated that the excreted dose was the equivalent of 250 to 330 micrograms of pseudoephedrine base, or 0.5 to 0.7% of the dose ingested by the mothers. Triprolidine did not appear to be concentrated in breast milk. The amounts of pseudoephedrine and triprolidine distributed into breast milk were probably not high enough to warrant cessation of breast feeding.

A small, randomised, crossover study concluded that a single dose of 60 mg pseudoephedrine hydrochloride decreased 24-hour milk production by 24%. The authors of the study suggested that pseudoephedrine might be of benefit for suppressing excess milk production.[3]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 05/01/07)
2. Findlay JWA, *et al.* Pseudoephedrine and triprolidine in plasma and breast milk of nursing mothers. *Br J Clin Pharmacol* 1984; 18: 901–6.
3. Aljazaf K, *et al.* Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *Br J Clin Pharmacol* 2003; 56: 18–24.

Convulsions. A child who suffered a generalised seizure after ingesting a large quantity of pseudoephedrine hydrochloride tablets was believed to be the first report of convulsions associated with overdose of a preparation containing the drug as a single ingredient.[1]

1. Clark RF, Curry SC. Pseudoephedrine dangers. *Pediatrics* 1990; 85: 389–90.

Effects on the gastrointestinal tract. Ischaemic colitis has been reported[1-3] after acute or chronic use of pseudoephedrine in combination cold and allergy preparations. In one case[3] the authors suggested that use with tramadol may have contributed to adrenergic vasoconstriction by inhibition of noradrenaline reuptake.

1. Dowd J, *et al.* Ischemic colitis associated with pseudoephedrine: four cases. *Am J Gastroenterol* 1999; 94: 2430–4.
2. Lichtenstein GR, Yee NS. Ischemic colitis associated with decongestant use. *Ann Intern Med* 2000; 132: 682.
3. Traino AA, *et al.* Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. *Ann Pharmacother* 2004; 38: 2068–70.

Effects on mental function. Adverse mental effects (particularly in children) have been associated with combination preparations containing pseudoephedrine.[1-5] See also Abuse, above.

1. Leighton KM. Paranoid psychosis after abuse of Actifed. *BMJ* 1982; 284: 789–90.
2. Sankey RJ, *et al.* Visual hallucinations in children receiving decongestants. *BMJ* 1984; 288: 1369.
3. Stokes MA. Visual hallucinations in children receiving decongestant. *BMJ* 1984; 288: 1540.
4. Roberge RJ, *et al.* Dextromethorphan and pseudoephedrine-induced agitated psychosis and ataxia: case report. *J Emerg Med* 1999; 17: 285–8.
5. Soutullo CA, *et al.* Psychosis associated with pseudoephedrine and dextromethorphan. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 1471–2.

Effects on the skin. Recurrent pseudo-scarlatina has been described in a female patient and attributed, on some occasions at least, to ingestion of pseudoephedrine. Further fixed drug eruptions associated with pseudoephedrine have been reported.[2-4] In another woman, an erythematous macular rash developed 5½ hours after an oral challenge with pseudoephedrine 60 mg; other symptoms, which mimicked the effects of toxic shock syndrome, included nausea and vomiting, fever, orthostatic hypotension, light-headedness, fatigue, and desquamation of the skin on her palms and soles.[3] However, considering the frequent use of pseudoephedrine in over-the-counter medications, associated drug eruptions generally appear to be rare.[2]

1. Taylor BJ, Duffill MB. *Br J Dermatol* 1988; 118: 827–9.
2. Camisa C. Fixed drug reactions to pseudoephedrine hydrochloride. *Br J Dermatol* 1989; 120: 857–8.
3. Cavanah DK, Ballas ZK. Pseudoephedrine reaction presenting as recurrent toxic shock syndrome. *Ann Intern Med* 1993; 119: 302–3.
4. Rauken M. Fixed drug eruption and pseudoephedrine. *Ann Intern Med* 1994; 120: 442.

Paediatric mortality. In response to reports in the USA of overdosages associated with cough and cold medications the CDC and the National Association of Medical Examiners investigated deaths in infants aged under 12 months associated with such use; 3 cases were identified. All 3 infants had high concentrations of pseudoephedrine in postmortem blood samples, 2 had detectable blood concentrations of dextromethorphan and paracetamol, and 1 was also found to have detectable concentrations of doxylamine. None of the deaths were determined to be intentional. Two infants had evidence of respiratory infection upon autopsy; no cardiac abnormalities were found in any of the infants.[1]

1. CDC. Infant deaths associated with cough and cold medications—two States, 2005. *MMWR* 2007; 56: 1–4. Also available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5601a1.htm (accessed 19/04/07)

Pregnancy. During pregnancy taking pseudoephedrine with paracetamol has been suggested to increase the risk of gastroschisis (defective closure of the abdominal wall) in newborns.[1] Although the evidence for this is weak, it is advisable that pseudoephedrine should be avoided during pregnancy because of the severity of the abnormality and the availability of alternatives to pseudoephedrine.

1. Werler MM, *et al.* Maternal medication use and risks of gastroschisis and small intestinal atresia. *Am J Epidemiol* 2002; 155: 26–31.

Tolerance. In 34 healthy males given pseudoephedrine 120 or 150 mg twice daily for 7 days, as a modified-release preparation, mean plasma concentrations were about 450 or 510 nanograms/mL, respectively. Adverse effects (dry mouth, anorexia, insomnia, anxiety, tension, restlessness, tachycardia, palpitations) were common; there was some evidence of tachyphylaxis.[1]

1. Dickerson J, *et al.* Dose tolerance and pharmacokinetic studies of L(+)-pseudoephedrine capsules in man. *Eur J Clin Pharmacol* 1978; 14: 253–9.

Interactions

As for Ephedrine, p. 1664.2. Pseudoephedrine may cause a hypertensive crisis in patients receiving a MAOI (including a RIMA). For additional warnings see under phenelzine (p. 445.1) and moclobemide (p. 438.1). For mention of a possible interaction between pseudoephedrine and tramadol, see Effects on the Gastrointestinal Tract, above.

Antacids. The absorption rate of pseudoephedrine hydrochloride was increased by *aluminium hydroxide* mixture but

was decreased by *kaolin*; in the latter case adsorption may have competed with absorption.[1]

1. Lucarotti RL, *et al.* Enhanced pseudoephedrine absorption by concurrent administration of aluminium hydroxide gel in humans. *J Pharm Sci* 1972; 61: 903–5.

Vaccines. A 21-year-old mildly obese man taking pseudoephedrine in an over-the-counter formulation for weight loss collapsed and died with a core temperature of 42.2 degrees while exercising, shortly after inoculation with *Japanese encephalitis vaccine* and *typhoid vaccine*.[1] The combined effects of the pseudoephedrine, activity, and the pyrogenic action of the vaccines appeared to have contributed to failure of the thermoregulatory system.

1. Franklin QJ. Sudden death after typhoid and Japanese encephalitis vaccination in a young male taking pseudoephedrine. *Mil Med* 1999; 164: 157–9.

Pharmacokinetics

Pseudoephedrine is readily absorbed from the gastrointestinal tract. It is excreted largely unchanged in the urine with small amounts of its hepatic metabolite. It has a half-life of about 5 to 8 hours; elimination is enhanced and half-life accordingly shorter in acid urine. Small amounts are distributed into breast milk.

References.
1. Simons FER, *et al.* Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr* 1996; 129: 729–34.
2. Chester N, *et al.* Elimination of ephedrines in urine following multiple dosing: the consequences for athletes, in relation to doping control. *Br J Clin Pharmacol* 2004; 57: 62–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Aseptobron Descongestivo; Mex; Qura Plus; ***Austral.***: Chemists Own Sinus Relief; Dimetapp Sinus†; Logicin Sinus; Sudafed Sinus & Nasal Decongestant†; Sudafed†; ***Belg.***: Otrivine Nasa-Tab†; Rinomart†; Vasocedine Pseudoephedrine; ***Canad.***: Benylin D†; Benylin DM-D-E-A Cold and Sinus; Cold and Flu-in-One; Congest Aid†; Decon†; Drixoral ND†; Eltor; Non Drowsy Contac Cold 12 Hour†; Non Drowsy Regular Strength Contac Cold 12 Hour†; Pseudofrin; Sudafed Decongestant; Tantafed; ***Chile***: Dexan; ***China***: Ai Qing (艾清); De Li Tong (德力通); Long Sha (龙沙); Tong Shu (同舒); Cz.: Nurofen Stopgrip; ***Fr.***: Sudafed; ***Hong Kong***: Logicin Sinus; Syncodrin†; Uni-Sufed†; Vicodrine†; Vidadrine†; ***India***: Dolcy; Sudafed; ***Indon.***: Alco; Disudrin; Neo Triaminic; Rhinos Neo; Sudafed†; ***Irl.***: Decongestant; Meltus Decongestant†; Sudafed Non-Drowsy Decongestant; Zirtek Plus; ***Israel***: Afalpi; Kalsinus; Sinufed; Tarophed†; ***Ital.***: Narixan; ***Mex.***: Dofedrin†; Sudafed†; ***NZ***: Sudafed 12 Hour Relief†; Sudafed Sinus & Nasal Decongestant†; Sudomyl; ***Pol.***: Sudafed; ***Port.***: Contac; Sudafed; ***S.Afr.***: Acunaso; Adco-Sufedrin; Adco-Symptofed; Drilix; Drinasal S†; Sinumed; Sudafed Sinus†; ***Singapore***: Contac Non Drowsy; Pseudorine; Sudafed; ***Spain***: Neo Durasina†; Reactine Plus†; ***Switz.***: Otrinol†; ***Turk.***: Dekoferin; Eksofed; Rinogest; Sudafed; ***UAE***: Sedofan II; ***UK***: Contac Non Drowsy; Galpseud; Meltus Decongestant; Non-Drowsy Sudafed Decongestant; ***Ukr.***: Daleron Cold 3 (Далерон Колд 3); ***USA***: Afrin; Allermed; Cenafed†; Childrens Sudafed Nasal Decongestant; Congestaid; Decofed†; DeFed; Dimetapp Decongestant†; Dorcol Children's Decongestant; Drixoral Non-Drowsy Formula†; Efidac 24 Pseudoepehdrine†; ElixSure Childrens Congestion; Genaphed; Halofed; Kid Kare Pediatric Nasal Decongestant; Medi-First Sinus Decongestant†; Mini Pseudo; Nasofed†; PediaCare Infant's Decongestant†; Pseudo-Gest; Pseudo; Seudotabs; Silfedrine†; Simply Stuffy; Sinustop Pro; Sudafed Non-Drowsy; SudoGest Non-Drowsy; Triaminic Allergy Congestion†; Unifed; Zephrex-D.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
BP 2014: Pseudoephedrine Oral Solution; Pseudoephedrine Tablets;
USP 36: Acetaminophen and Pseudoephedrine Hydrochloride Tablets; Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution; Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets; Cetirizine Hydrochloride and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Extended-release Capsules; Chlorpheniramine Maleate and Pseudoephedrine Hydrochloride Oral Solution; Dexbrompheniramine Maleate and Pseudoephedrine Sulfate Oral Solution; Diphenhydramine and Pseudoephedrine Capsules; Fexofenadine Hydrochloride and Pseudoephedrine Hydrochloride Extended-Release Tablets; Guaifenesin and Pseudoephedrine Hydrochloride Capsules; Guaifenesin, Pseudoephedrine Hydrochloride, and Dextromethorphan Hydrobromide Capsules; Ibuprofen and Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride Extended-Release Capsules; Pseudoephedrine Hydrochloride Extended-release Tablets; Pseudoephedrine Hydrochloride Syrup; Pseudoephedrine Hydrochloride Tablets; Pseudoephedrine Hydrochloride, Carbinoxamine Maleate, and Dextromethorphan Hydrobromide Oral Solution; Triprolidine and Pseudoephedrine Hydrochlorides Syrup; Triprolidine and Pseudoephedrine Hydrochlorides Tablets.

Senega Root

Észak-amerikai-szenegagyökér; Polígala Raíz; Polygala, racine de; Polygalae Radix; Putoklių šaknys; Raíz de polígala; Rattlesnake Root; Seneca Snakeroot; Senega; Seneganjuuri; *Senegarot*; Senegawurzel; *Vitodový kořen*; Истод Сенега.
ATC — R05CA06.
ATC Vet — QR05CA06.
ATC Herb — HR05WA5042 (Polygala senega: root).
UNII — M7T6H7D4IF.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn*.

Jpn also describes the powdered root.

Ph. Eur. 8: (Senega Root). The dried and usually fragmented root and root crown of *Polygala senega* or certain closely related species of *Polygala* or a mixture of these. It has a faint, sweet odour, slightly rancid or reminiscent of methyl salicylate. Protect from light and humidity.

Profile

Senega root has been used as an expectorant in oral preparations for respiratory-tract disorders.

Polygala amara is a related species that is used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Hebert Caramelos; Ixana; Ixana; No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pectobron; ***Austral.***: Asa Tones†; Nyal Night-Time Cough; Senega and Ammonia; ***Austria***: Eicebaer; Tussimont; ***Belg.***: Saintbois; ***Braz.***: Expectomel; Melagriao; ***Canad.***: Bronchial Cough; Sirop Cocillana Codeine; ***Fr.***: Neo-Codion; NurAiD; ***Hong Kong***: Coci-Fedra-C†; Coci-Fedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinllana†; Coolding†; Dextrocilla; Eurocilana; Mist Expect Stim†; ***India***: Elixir Efelin; ***Ital.***: Altuss; ***Port.***: Stodal; ***Rus.***: Neo-Codion Babies (Нео-Кодион Для Младенцев)†; ***S.Afr.***: Borstol Cough Remedy†; ***Singapore***: NeuroAid; ***Spain***: Pastillas Pectorales Kely†; Pulmofasa; ***Swed.***: Cocillana-Etyfin; ***Switz.***: Hederix; Liberol Pastilles contre la toux†; Liberol Sirop contre la toux†; Makaphyt Gouttes antitussives†; Makaphyt Sirop†; Pastilles pectorales du Dr. Welti; Pectocalmine N; Pectoral N; Phol-Tux; Siropectan; ***Thai.***: Mist Scill Ammon; Squill and Ammonia; ***UK***: Antibron; Chest Mixture; Chesty Cough Relief; Tickly Cough & Sore Throat Relief; ***Ukr.***: Pectoral (Пекторал); ***Venez.***: Acetoben; Dromil Sauco; Novacodin; Yerba Santa.

Homoeopathic Preparations. ***Austral.***: Respatona Chesty Cough & Nasal Congestion; ***Austria***: Globuli gegen Husten Nr 2; ***Canad.***: L52 Cough & Cold; ***Cz.***: Lehnigrip†; Stodal; ***Fr.***: Boripharm No 11†; Ipeca Complexe No 65; L 52; Stodal; ***Ger.***: Infigripp.

Sobrerol

Ciclidrol; Cyclidrol; Sobreroli; Sobrerolo; Sobrerolum; Собророл.
p-Menth-6-ene-2,8-diol.
$C_{10}H_{18}O_2$=170.3
CAS — 498-71-5.
ATC — R05CB07.
ATC Vet — QR05CB07.
UNII — AIONX02O35.

Pharmacopoeias. In *It.*

Profile

Sobrerol is a mucolytic that has been used in respiratory disorders characterised by productive cough (p. 1651.2). Oral doses of up to 600 mg have been given daily in divided doses. Sobrerol has also been given by injection, inhalation, or rectally.

Pharmacokinetics. The pharmacokinetics of sobrerol after oral or intravenous doses has been studied in patients with acute exacerbations of chronic bronchitis.[1] Sobrerol was rapidly absorbed from the gastrointestinal tract and rapidly distributed. After intravenous and oral dosage, 13 and 23% of the dose respectively was excreted in the urine as unchanged drug, glucuronidated sobrerol, and hydrated carvone. Sobrerol was shown to accumulate in bronchial mucus.

1. Braga PC, *et al.* Pharmacokinetics of sobrerol in chronic bronchitis: comparison of serum and bronchial mucus levels. *Eur J Clin Pharmacol* 1983; 24: 209–15.

Respiratory disorders. References.
1. Bellussi L, *et al.* Evaluation of the efficacy and safety of sobrerol granules in patients suffering from chronic rhinosinusitis. *J Int Med Res* 1990; 18: 454–9.
2. Azzollini E, *et al.* Sobrerol (Sobrepim) administered dropwise to children with acute hypersecretory bronchopulmonary disease: a controlled trial v bromhexine. *Clin Trials J* 1990; 27: 241–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Sobrepin; ***Hong Kong***: Mucoflux; ***Ital.***: Sobrepin; Sopulmin; ***Malaysia***: Mucoflux; ***Philipp.***: Mucoflux; ***Port.***: Mucodox; Pulmus; ***Singapore***: Mucoflux; ***Spain***: Sobrepin; ***Thai.***: Mucoflux.

Multi-ingredient Preparations. ***Gr.***: Carbozor; Flemagon; Grupozil; Gutman; Mucostein; Pneumol Plus; Polimucil; Respinorm; Sevlenyl; Sobrein; Sorbexyl; Tussifren; Vanesin; ***Ital.***: Fluental; ***Port.***: Bronquial; Niflux.

Sodium Dibunate *(BAN, rINN)*

Dibunate de Sodium; Dibunato de sodio; L-1633; Natrii Dibunas; Натрий Дибунат.
Sodium 2,6-di-*tert*-butylnaphthalene-1-sulphonate.
$C_{18}H_{23}NaO_3S$=342.4
CAS — 14992-59-7 (sodium dibunate).
ATC — R05DB16.
ATC Vet — QR05DB16.
UNII — FRS4SO3K8D.

Profile

Sodium dibunate is a cough suppressant given orally and rectally in non-productive cough. It is claimed to have central and peripheral actions. Chlorcyclizine dibunate (naftodizine) has also been given similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Dibunafon; ***Port.***: Becantex.

Multi-ingredient Preparations. ***Braz.***: Beclase†; ***Ger.***: Ephepect-Blocker-Pastillen N; ***Hong Kong***: Ephepect Blocker; ***Mex.***: Broend; Neo-Brontyl†; ***Ukr.***: Bronchobru (Бронхобрю).

Squill

Bulbo de Escila; Cebolla Albarrana; Cila; Escila; Meerzwiebel; Scilla; Scillae bulbus; Scille; Scille, bulbe de; White Squill; Морской Лук.

Pharmacopoeias. In *Br.* and *Ger.*

BP 2014: (Squill). The dried sliced bulb of *Drimia maritima* with the membranous outer scales removed, and containing not less than 68% of alcohol (60%)-soluble extractive. Store at a temperature not exceeding 25 degrees in a dry place.

Indian Squill

Escila India; Urginea; Морской Лук Индийский.
ATC Herb — HR05WA5006 (Drimia maritima: bulb); HG048W5009 (Drimia maritima: bulb); HC01AB5001 (Drimia maritima: bulb).

Pharmacopoeias. In *Br.*

BP 2014: (Indian Squill). The bulb of *Drimia indica*, with the outer membranous scales removed, usually sliced and dried. Store at a temperature not exceeding 25 degrees in a dry place.

Uses and Administration

Squill and Indian squill are used as expectorants in productive cough and have been given as the oxymel, elixir, tincture, or vinegar. Preparations containing squill are used in some countries in the treatment of cardiovascular disorders.

Red squill has been used as a rodenticide (p. 2161.2).

The historical use of squill has been reviewed.[1]

1. Allorta G, *et al.* The diuretic use of Scilla from Dioscorides to the end of the 18th century. *J Nephrol* 2004; 17: 342–7.

Adverse Effects, Treatment, and Precautions

The adverse effects of squill and Indian squill in large doses include nausea, vomiting, and diarrhoea. As squill and Indian squill contain cardiac glycosides they can cause similar adverse effects to digoxin (p. 1354.3).

Abuse. Reports of cardiac glycoside toxicity and myopathy associated with the abuse of linctuses that have contained opiates and squill.[1-5]

1. Kennedy M. Cardiac glycoside toxicity: an unusual manifestation of drug addiction. *Med J Aust* 1981; 2: 686–9.
2. Kilpatrick C, *et al.* Myopathy with myasthenic features possibly induced by codeine linctus. *Med J Aust* 1982; 2: 410.
3. Seow SSW. Abuse of APF linctus codeine and cardiac glycoside toxicity. *Med J Aust* 1984; 140: 54.
4. Thurston D, Taylor K. Gee's Linctus. *Pharm J* 1984; 233: 63.
5. Smith W, *et al.* Wenckebach's phenomenon induced by cough linctus. *BMJ* 1986; 292: 868.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Ixana; *Austral.*: Nyal Night-Time Cough; *Canad.*: Bronco Asmol†; Herbal Cough Syrup†; Sirop Cocillana Codeine; *Ger.*: Miroton†; *Hong Kong*: Coci-Pedra-C†; Coci-Pedra†; Cocillana Christo; Cocillana Co w/o Codeine†; Cocillana Co†; Cocillana Compound (Non-Narcotic)†; Cocillana Compound with Codeine†; Cocillana Compound†; Cocillana Compound; Codeinillana†; Compound Cocillana†; Cooldingt†; Dextrocilla; Ephecol†; Eurocilana; Fritussin†; Mist Expect Stim†; *Mex.*: Verisan Triplex; *S.Afr.*: Adco-Cocillana Co; Contra-Coff†; Linctus Tussi Infans†; *Thai.*: Mist Scill Ammon; Squill and Ammonia; *UK*: Allens Chesty Cough; Allens Pine & Honey; Balm of Gilead†; Buttercup Syrup; Chest Mixture; Covonia Herbal Mucus Cough Syrup; Covonia Mentholated; Galloway's Cough Syrup; Honey & Molasses; Modern Herbals Cough Mixture; Potters Children's Cough Pastilles; Potters Gees Linctus; Quitacoff; Sanderson's Throat Specific; Sanderson's Throat Specific.

Homoeopathic Preparations. *Austria*: Homviocorin; *Canad.*: Husteel†; Valerianaheel Comp†; *Cz.*: Husteel; *Ger.*: Confludin N; Cor-loges; Corvipas SL; Lowe-Komplex Nr 13; Lymphdiaral; Truw Gold; Uroselect; *Hung.*: Husteel; *Neth.*: Asthmakhell†; Husteel; *Ukr.*: Homviocorin-N (Хомвиокорин-N).

Pharmacopoeial Preparations
BP 2014: Squill Liquid Extract; Squill Oxymel.

Sulfogaiacol *(rINN)*

Kalli Sulfoguajacolas; Kalium Guajacolsulfonicum; Kaliumsulfoguajakolaatti; Kaliumsulfoguajakolat; Potassium Guaiacolsulfonate; Potassium Guaiacolsulphonate; Sulfogaïacol; Sulfogaiacolum; Sulfoguayacol; Sulfogwajakol; Thiocol; Tiocol; Сульфогайякол.

Potassium hydroxymethoxybenzenesulphonate hemihydrate.

$C_7H_7KO_5S,½H_2O=251.3$

CAS — 1321-14-8 (anhydrous sulfogaiacol); 78247-49-1 (sulfogaiacol hemihydrate).

ATC — R05CA09.

ATC Vet — QR05CA09.

UNII — 713AJ00NPG (sulfogaiacol); TTK33Z47F1 (sulfogaiacol hemihydrate).

Pharmacopoeias. In *Pol.* and *US.* Also in *Fr.* and *Jpn*, both of which do not specify the hemihydrate.

USP 36: (Potassium Guaiacolsulfonate). Protect from light.

Profile

Sulfogaiacol is used as an expectorant for productive cough. Calcium guaiacolsulfonate has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pectoral Lafedar Ninos; *Austria*: Pectosorin†; *China*: Kang Yu Deng Tong (康裕登通); *Israel*: Guaiacol; *Ital.*: Tioguaialina; *Mex.*: Broncoserum; *Pol.*: Apitussic; Diabetussic.

Multi-ingredient Preparations. *Arg.*: Medex Rub; No-Tos Infantil; No-Tos Infantil; Pastillas De Ambay; Pectobron; Pectoral Lafedar; *Austria*: Pneumopan†; *Belg.*: Broncho-pectoralis Pholcodine; Eucalytux; Pholco-Mereprine; Saintbois; *Braz.*: Broncatar; Expectil; Fenergan Expectorante; Iodetal; Trifedrin; *China*: Ke Li An (克立安); Norpin A (纳尔平); Xin Tai Luo Qi (新泰洛其); *Fr.*: Camphodionyl†; Ephydion†; Neo-Codion; Passedyl; Pneumaseptic†; *Hong Kong*: Chrisracol; Ephecol†; *Hung.*: Erigon; *India*: Pulm-Cod (C & G); *Indon.*: Benacol DTM; Benacol Expectorant; Febrinex; Phenacold; Phenadex; Prome; Promethazine Ikapharmindo; Sanadryl; *Israel*: Cod-Guaiacol; Oxacatin; Pertussol; Promethazine Expectorants; To-Care; Tucare; Tussophedrine NF; *Ital.*: Balsamina Kroner; Bronchenolo; Bronchiase; Donalg; Guaiacalcium Complex; Polised; Sciroppo Berta; Stenobronchial; Tauglicolo; Tiocalmina; Tiocosol†; *Mex.*: Eucaliptine†; Exofil; Oxin; Pulmovital; *Philipp.*: Cofrel; *Pol.*: Apipulmol; Gwajatussin; Herbapect; Pastylki Wykrztusne; Thiocodin; *Port.*: Codol; *Rus.*: Neo-Codion (Нео-Кодион)†; *Spain*: Bronco Medical; Broncovir; Brota Rectal Balsamico†; Fenergan Expectorante; Pastillas Pectorales Kely†; Pazbronquial; Pulmofasa; *Switz.*: Neo-Codion N; Phol-Tux; *Thai.*: Bisolvon EX; Bromso-Ex; Dutross-P; Hustazol-C; *Turk.*: Antibeksin; Artu; Fenokodin†; Gayabeksin; Gayaben; Latusin†; Pektodin†; Seskadeks; *Ukr.*: Tos-Mai (Тос-Май); *USA*: Cypex; De-Chlor NX†; Entuss Expectorant; Humibid DM; Humibid; Hy-KXP†; Hydron EX†; Hydron KGS†; KGS-PE; Lemotussin-DM; Marcof†; Prolex DM†; Prolex DMX†.

Talniflumate *(USAN, rINN)*

BA-7602-06; Talniflumato; Talniflumatum; Тальнифлумат.

Phthalidyl 2-(α,α,α-trifluoro-*m*-toluidino)nicotinate.

$C_{21}H_{13}F_3N_2O_4=414.3$

CAS — 66898-62-2.

UNII — JFK785OU9S.

NOTE. The name Lomucin has been used as a trade mark for talniflumate.

Profile

Talniflumate inhibits the human calcium-activated chloride channel protein hCLCA1, which is overexpressed in the lungs of patients with certain pulmonary diseases associated with excessive or abnormal mucus production. Talniflumate has been investigated for the management of cystic fibrosis, chronic obstructive pulmonary disease, and asthma. Talniflumate has also been used to treat inflammation.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Somalgen.

Telmesteine *(rINN)*

Telmesteína; Telmestéine; Telmesteinum; Тельместеин.

(-)-3-Ethyl hydrogen (*R*)-3,4-thiazolidinedicarboxylate.

$C_7H_{11}NO_4S=205.2$

CAS — 122946-43-4.

UNII — 124I3FE35T.

Profile

Telmesteine has been used as a mucolytic in the treatment of respiratory-tract disorders including cough (p. 1651.2) in oral doses of 300 mg two or three times daily.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Reolase.

Multi-ingredient Preparations. *Austral.*: Atopiclair†; *Indon.*: Atopiclair; *Israel*: Atopiclair; Xclair; *Singapore*: Atopiclair; *UK*: Atopiclair; Xclair; *USA*: Atopiclair.

Terpin Hydrate *(BANM)*

Terpene Hydrate; Terpiinihydraatti; Terpina, hidrato de; Terpinhydrat; Terpini Hydras; Terpinol; Терпингидрат.

p-Menthane-1,8-diol monohydrate; 4-Hydroxy-α,α,4-trimethylcyclohexanemethanol monohydrate.

$C_{10}H_{20}O_2.H_2O=190.3$

CAS — 80-53-5 (anhydrous terpin); 2451-01-6 (terpin monohydrate).

UNII — S3V8685487.

Pharmacopoeias. In *Fr., Swiss, US,* and *Viet.*

USP 36: (Terpin Hydrate). Colourless lustrous crystals or white powder with a slight odour. It effloresces in dry air. Soluble 1 in 200 of water, 1 in 35 of boiling water, 1 in 13 of alcohol, 1 in 3 of boiling alcohol, and 1 in 140 of chloroform and of ether. A hot 1% solution is neutral to litmus. Store in airtight containers.

Stability. If crystals form in terpin hydrate elixir, they may be redissolved by warming the closed container of solution in warm water and then gently shaking it.

Profile

Terpin hydrate has been stated to increase bronchial secretion directly and has been given orally as an expectorant in productive cough.

Nausea, vomiting, or abdominal pain may follow the ingestion of terpin hydrate on an empty stomach.

Terpin hydrochloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Alma; *India*: Haffkinol.

Multi-ingredient Preparations. *Arg.*: Aseptobron; *Braz.*: Ozonyl; Tetrapulmo†; *Chile*: Broncodeina; *Cz.*: Coldrex; *Fin.*: Toclase Expectorant†; *Fr.*: Bronchorectine au Citral; Euphonyl Expectorant; Pulmofluide Simple; Pulmoll†; Terpine Gonnon; Terpone; Thiopectol; *Hong Kong*: Chrisracol; Codoplex; Coldcap-A; Coldtab-2; Panadol Cold & Flu Day; Panadol Cold & Flu Extra Panadol Cold & Flu; *Hung.*: Coldrex; *India*: Benakof; Cadistir Exp; Glycodin; *Ital.*: Elisir Terpina; Neo Borocillina Balsamica *Neth.*: Balsoclase Compositum†; *Pol.*: Coldrex MaxGrip C; *Rus.* Alex Plus (Алекс Плюс); Coldrex (Колдрекс); Flucoldex Forte (Флюколдекс Форте); Glycodin (Гликодин); Tedein (Тедеин) Tercodin (Теркодин); Terpincod (Терпинкод); *Spain*: Pastilla Pectorales Kely†; Terponil†; *Switz.*: Bromocod N†; Rectoseptal Neo bismuthe; Rectoseptal-Neo simple; *Thai.*: Antust; Codee-C Cophartussin; CPM; D-Coate; Decofsin; Dexpin; Dextro Compound; Dextro; Dextrussin; Dimophen; Fartussin; Glycoff; Icolic DX; Methopine; Mila-Tercon†; Muco-DX†; Rocal; Seco; Sinfussi; Stocof; Stocol; Terco-C; Terco-D; Terracol-A; Tusspac; *Turk.* Tusifon; *UK*: Original Cabdrivers Expectorant; *Ukr.*: Alex Plus (Алекс Плюс)†; Coldrex (Колдрекс); Glycodin (Гликодин).

Pharmacopoeial Preparations
USP 36: Terpin Hydrate and Codeine Elixir; Terpin Hydrate Elixir.

Tetryzoline Hydrochloride *(BANM, rINNM)* ⊗

Hidrocloruro de tetrahidrozolina; Hidrocloruro de tetrizolina; Tetrahydrozoline Hydrochloride; Tetrazolin Hidroklorür; Tetrizolina, hidrocloruro de; Tetrizolino hidrochloridas; Tetrytsoliinihydrokloridi; Tétryzoline, Chlorhydrate de; Tetryzolin-hydrochlorid; Tetryzolinhydrochlorid; Tetryzolinhydroklorid; Tetryzolini Hydrochloridum; Тетризолина Гидрохлорид.

2-(1,2,3,4-Tetrahydro-1-naphthyl)-2-imidazoline hydrochloride.

$C_{13}H_{16}N_2.HCl=236.7$

CAS — 84-22-0 (tetryzoline); 522-48-5 (tetryzoline hydrochloride).

ATC — R01AA06; R01AB03; S01GA02.

ATC Vet — QR01AA06; QR01AB03; QS01GA02.

UNII — 0YZT43HS7D.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tetryzoline Hydrochloride). A white or almost white crystalline powder. Freely soluble in water, in alcohol, and in dehydrated alcohol; practically insoluble in acetone.

USP 36: (Tetrahydrozoline Hydrochloride). A white odourless solid. Soluble 1 in 3.5 of water and 1 in 7.5 of alcohol; very slightly soluble in chloroform; practically insoluble in ether. Store in airtight containers.

Profile

Tetryzoline is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It is used as the hydrochloride for its vasoconstrictor effect in the symptomatic relief of nasal congestion (p. 1652.1). A 0.1% solution is instilled into each nostril as nasal drops or a spray as necessary, although not more often than every 3 hours. A lower strength solution of 0.05% is also available.

Solutions of tetryzoline hydrochloride containing 0.05% have been used as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Other salts of tetryzoline including the nitrate, phosphate, and sulfate have been used similarly.

Abuse. Tetryzoline ophthalmic solution 0.05% has been given orally in drug facilitated sexual assault to obtain an obtunded flaccid victim who is unable to resist or recall events.[1]

1. Spiller HA, *et al.* Drug facilitated sexual assault using an over-the-counter ocular solution containing tetrahydrozoline (Visine). *Leg Med (Tokyo)* 2007; 9: 192–5.

Effects on the eyes. For mention of conjunctivitis induced by ophthalmic decongestant preparations containing tetryzoline, see under Phenylephrine, p. 1673.2.

Poisoning. A 17-year-old girl who ingested about 10 to 15 mL of a 0.05% solution of tetryzoline by mistake developed lethargy, slowed speech and ataxia.[1] She also complained of dizziness, headache, and sinus congestion. Drowsiness, bradycardia, and orthostatic hypotension were apparent up to 36 hours post-ingestion.

1. Spiller H, Griffith J. Prolonged cardiovascular effects after unintentional ingestion of tetrahydrozoline. *Clin Toxicol* 2008; 46: 171–2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bano Ocular; Chiosan; Irix; Ocudiafan; Piam; Visubril; *Austral.*: Murine Sore Eyes; Visine Clear; *Belg.*: Visine; *Canad.*: Eye Drops; Original Eye Drops; Visine Original; *Chile*: Visine; Visional Gotas; *Cz.*: Rhinal†; Vasopos N; Visine; *Denm.*: Visine Visiclear; *Fin.*: Oftan Starine; Visclear; *Ger.*: Ophtalmin N; Tetrilin; Vasopos N; Visine Yxin; *Gr.*: Octilia; Ursa-Fin; Visine; Vispring; *Hong Kong*: Murine Plus†; Optizoline; Visine Original†; *Hung.*: Tyzine†; Visine; *India*: Visine†; *Indon.*: Braito†; Insto; Isotic Clearin†; Santo; Visine; Visolin†; Visto; *Israel*: Azoline; Eye Relief; Stilla; V-

Zoline; View; Visine; *Ital.*: Demetil; Eyedec; Octilia; Stilla Decongestionante; Stilla Unidose; Vasorinil; *Jpn*: Narbel; *Malaysia*: Allersine; Visine†; *Mex.*: Eye-Mo; Tetrazol; *NZ*: Visine; *Philipp.*: Eye-Mo; Sinutab NS; Visine Advanced Relief†; Visine Cool†; Visine; Visol; *Pol.*: Berberil; Starazolin; Tetryvil†; Visine; *Port.*: Visine; *Rus.*: Montevizin (Монтевизин); Octilia (Октилия); Tyzine (Тизин); Visine (Визин); Vizoptik (Визоптик); *S.Afr.*: Visine; *Singapore*: Optizoline; *Spain*: Azulina; Vispring; *Switz.*: Rhinopront Top†; Visine; *Thai.*: Visine†; *Turk.*: Burnil; Eye-Visol; Visine; Zenkain†; *Ukr.*: Tyzine (Тизин); Vial (Виаль); Visine (Визин); *USA*: Eye Drops; Eye-Zine; Optigene 3; Tyzine; Visine Original.

Multi-ingredient Preparations. *Arg.*: Antiflogol; Efemolina; Larsimal; Provisual Compuesto; Toflam Plus; Visine Plus; *Austral.*: Visine Advanced Relief; *Braz.*: Fenidex; Mirabel; Vislin; Visodin; *Canad.*: Allergy Eye Drops; Clear Eyes Triple; Visine Advance Triple Action; Visine Allergy; Visine Cool; *Chile*: Spersallerg; *Cz.*: Spersallerg; *Ger.*: Allergopos N†; Berberil N; Efemolin†; Spersallerg†; *Gr.*: Efemoline; Spersadexoline; Spersallerg; *Hong Kong*: Efemoline; Murine Plus Natural†; Spersallerg; Visine AC†; Visine Moisturizing†; *Hung.*: Spersallerg; *India*: Optihist-Plus; *Indon.*: Visine Extra; *Israel*: Visine AC; *Ital.*: Biorinil; Cromozil; Efemoline; Eta Biocortilen VC; Flumezina; Ischemol A; Stillergy; Tetramil; Visublefarite; Visucloben Decongestionante; Visumetazone Antibiotico; Visumetazone Decongestionante; Visustrin; *Malaysia*: Gentadexa; Spersadexoline†; Spersallerg; *Mex.*: Fluorometil; Visine Extra; *Norw.*: Spersallerg; *NZ*: Visine Advanced Relief; *Philipp.*: Efemoline; Spersallerg; *Pol.*: Spersallerg; *Port.*: Gentadexa; *Rus.*: Spersallerg (Сперсаллерг); *S.Afr.*: Efemoline; Gemini; Oculerge; Spersadexoline†; Spersallerg; *Singapore*: Efemoline; Murine Plus; Spersadexoline; Spersallerg; *Spain*: Fluorvas; Gentadexa; Medrivas Antib; Medrivas; Tivitis†; Vasodexa; *Switz.*: Collypan; Efemoline; Spersallerg; *Thai.*: Allergis; Antazallerge; CD-Oph; Efemoline; Histaoph; Mano; Opsil-A; Spersadexoline†; Spersallerg; *Turk.*: Efemoline; Flumetol†; *USA*: Advanced Relief Visine; Geneye AC Allergy†; Murine Plus; Visine Maximum Redness Relief; Visine Totality Multi-Symptom Relief; *Venez.*: Gentidexa.

Pharmacopoeial Preparations
USP 36: Tetrahydrozoline Hydrochloride Nasal Solution; Tetrahydrozoline Hydrochloride Ophthalmic Solution.

Thebacon Hydrochloride *(BANM, rINNM)*

Acethydrocodone Hydrochloride; Acetyldihydrocodeinone Hydrochloride; Dihydrocodeinone Enol Acetate Hydrochloride; Hidrocloruro de tebacón; Tebacón, hidrocloruro de; Thébacone, Chlorhydrate de; Thebaconi Hydrochloridum; Тебакона Гидрохлорид.

6-*O*-Acetyl-7,8-dihydro-3-*O*-methyl-6,7-didehydromorphine hydrochloride; (-)-(5*R*)-4,5-Epoxy-3-methoxy-9a-methylmorphin-6-en-6-yl acetate hydrochloride.

$C_{20}H_{23}NO_4$,HCl=377.9

CAS — 466-90-0 (thebacon); 20236-82-2 (thebacon hydrochloride).

ATC — R05DA10.

ATC Vet — QR05DA10.

Profile

Thebacon hydrochloride is a centrally acting cough suppressant used for non-productive cough (p. 1651.2). It has actions similar to those of codeine (p. 40.2) but is stated to be about 4 times more potent. It is given orally in a usual daily dose of 10 mg in divided doses; the maximum daily dose should not exceed 20 mg.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Acedicone†.

Tipepidine Hibenzate *(rINNM)*

AT-327 (tipepidine); CR-662 (tipepidine); Hibenzato de tipepidina; Tipepidina, hibenzato de; Tipépidine, Hibenzate de; Tipepidine Hybenzate; Tipepidini Hibenzas; Типепидина Гибензат.

3-[Di(2-thienyl)methylene]-1-methylpiperidine 2-(4-hydroxybenzoyl)benzoate.

$C_{15}H_{17}NS_2$,$C_{14}H_{10}O_4$=517.7

CAS — 5169-78-8 (tipepidine); 31139-87-4 (tipepidine hibenzate).

ATC — R05DB24.

ATC Vet — QR05DB24.

UNII — 78578GFU8W.

Pharmacopoeias. In *Jpn.*

Profile

Tipepidine hibenzate is a cough suppressant used for non-productive cough (p. 1651.2) which is claimed also to have an expectorant action. It is given orally as the hibenzate but doses are expressed as the citrate; tipepidine hibenzate 22.2 mg is equivalent to about 20 mg of tipepidine citrate. A usual dose is the equivalent of 20 to 40 mg of the citrate 3 times daily.

Epileptogenic effect. Generalised convulsions associated with therapeutic oral doses of tipepidine hibenzate have occurred in some patients.[1]

1. Cuomo RM. On the possible convulsive activity of an antitussive piperidinic derivative ('tipepidina ibenzato') in man. *Acta Neurol (Napoli)* 1982; 37: 110–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Hong Kong*: Asverin†; *Indon.*: Asvex; *Jpn*: Asverin.

Multi-ingredient Preparations. *Arg.*: Di-Neumobron; *Indon.*: Neo Novapon Plus; Neo Novapon; *Jpn*: Sin Colgen Kowa Kaze†.

Tolu Balsam

Bálsamo de Tolú; Balsamum Tolutanum; Baume de Tolu; Tolú balzamas; Toluánský balzám; Tolubalsam; Tolubalzsam; Tolupalsami; Толуанский бальзам.

CAS — 9000-64-0; 8017-09-2.

ATC Herb — HR05WA5031 (Myroxylon balsamum var. balsamum: balsamo).

UNII — TD2LE91M8E.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Tolu Balsam). Oleoresin obtained from the trunk of *Myroxylon balsamum* var. *balsamum*. It contains 25 to 50% of free or combined acids, expressed as cinnamic acid, calculated with reference to the dried drug. It occurs as a hard, friable, brownish to reddish-brown mass; thin fragments are brownish-yellow when examined against the light. It has an odour reminiscent of vanillin. Practically insoluble in water and in petroleum spirit; very soluble or freely soluble in alcohol. *Do not store in powdered form.*

USP 36: (Tolu Balsam). A balsam obtained from *Myroxylon balsamum* (Leguminosae). It is a brown or yellowish-brown plastic solid transparent in thin layers and brittle when old, dried, or exposed to cold temperatures. It has a pleasant aromatic odour, resembling that of vanilla. Practically insoluble in water and in petroleum spirit; soluble in alcohol, in chloroform, and in ether, sometimes with slight residue or turbidity. Store at a temperature not exceeding 40 degrees in airtight containers.

Profile

Tolu balsam is considered to have very mild antiseptic properties and some expectorant action but is mainly used in the form of a syrup to flavour cough mixtures. However, Tolu Syrup (BP 2014) is based on cinnamic acid (p. 1748.3) and no longer contains tolu balsam.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: No-Tos Adultos; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pastillas Medex; Pastillas Pagliano; Pectobron; Refenax Caramelos Expectorantes; *Austral.*: Camphor Linctus Compound; *Belg.*: Saintbois; *Braz.*: Expectomel; Frenotosse; Glycon; Inhalante Yatropan; Iodetal; Melagriao; Vick Pastilhas†; *Canad.*: Bronco Asmol†; *Chile*: Elitos ET; Fitotos; Flemex Jat; Jarabe Palto Compuesto con Miel Adulto; Pulmosina; *Fr.*: Broncalene Nourisson†; Dinacode avec codeine; Hexapneumine†; Pastilles Medicinales Vicks; Pastilles Monleon†; Phytotux; Pulmosodyl; Terpine Gonnon; Thiopectol; Tussipax; *Hong Kong*: Baby Cough with Antihistamine†; Hexapneumine†; *India*: Cadistin Exp; *Ital.*: Stenobronchial; *Mex.*: Citos; Fen-y-Tos; *Port.*: Broncodiazina†; Stodal; *Rus.*: Solutan (Солутан)†; *S.Afr.*: Choats Extract of Lettuce Cough Mixture†; Linctus Tussi Infans†; Puma Cough Balsam†; Turulington Tincture†; *Spain*: Bactopumon; Bronquidiazina CR; Pulmofasa; *Switz.*: Baume Zeller; DemoPectol; Neo-Codion N; Phol-Tussil; Pommade au Baume; Rotpunkt Apotheke pastilles pour les bronches avec codeine; Sano Tuss; Siropectan; *Thai.*: Baby Cough Syrup Atlantic; Baby Cough with Antihistamine; *UK*: Allens Chesty Cough; Chesty Cough Relief; Modern Herbals Cold & Congestion; Sanderson's Throat Specific; *Ukr.*: Bronchial Balsam Bells (Бронхиальный Бальзам Белле); *USA*: Tonsiline; Vicks Menthol Cough Drops; *Venez.*: Yerba Santa.

Homoeopathic Preparations. *Cz.*: Stodal; *Fr.*: Stodal.

Pharmacopoeial Preparations
BPC 1954: Compound Iodoform Paint;
USNF 31: Tolu Balsam Syrup; Tolu Balsam Tincture;
USP 36: Compound Benzoin Tincture.

Tramazoline Hydrochloride

(BANM, USAN, rINNM) ⊗

Hidrocloruro de tramazolina; Tramazolina, hidrocloruro de; Tramazoline, Chlorhydrate de; Tramazolin-hidroklorid; Tramazolin-hydrochlorid; Tramazolini hydrochloridum; Tramazolino hidrochloridas; Tramazoliny chlorowodorek; Тразолина Гидрохлорид.

2-(5,6,7,8-Tetrahydro-1-naphthylamino)-2-imidazoline hydrochloride monohydrate.

$C_{13}H_{17}N_3$,HCl,H_2O=269.8

CAS — 1082-57-1 (tramazoline); 3715-90-0 (tramazoline hydrochloride).

ATC — R01AA09.

ATC Vet — QR01AA09.

UNII — 4DG710Q678.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Tramazoline Hydrochloride Monohydrate). A white or almost white crystalline powder. Soluble in water and in alcohol. A 5% solution in water has a pH of 4.9 to 6.3.

Profile

Tramazoline hydrochloride is a sympathomimetic with effects similar to those of naphazoline (p. 1669.3). It is used to provide symptomatic relief of nasal congestion (p. 1652.1). Tramazoline hydrochloride is given as a solution containing about 0.12%, instilled into each nostril as nasal drops or a spray three or four times daily.

Solutions of tramazoline hydrochloride containing about 0.06% have also been used in eye drops as a conjunctival decongestant (see Conjunctivitis, p. 611.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Spray-Tish; *Belg.*: Rhinospray; *Cz.*: Muconasal Plus; *Ger.*: Bidron; Ellatun; Rhinospray; *Ital.*: Rinogutt; *Neth.*: Bisolnasal; *Port.*: Rhinospray; *Rus.*: Rhinosprey (Риносприй); *Spain*: Rhinospray Eucalíptus; Rhinospray.

Multi-ingredient Preparations. *Arg.*: Dexa-Rhinospray N; *Austral.*: Spray-Tish Menthol; *Austria*: Rhinospray Plus; *Belg.*: Dexa-Rhinospray; *Ger.*: Dexa Bidron; Rhinospray Plus; *Gr.*: Dexa-Rhinaspray-N; Dexa-Rhinaspray; *Hung.*: Rhinospray Plus; *Irl.*: Dexa-Rhinaspray Duo†; *Ital.*: Rinogutt Antiallergico Spray; Rinogutt; *Neth.*: Rhinospray met eucalyptus; *Rus.*: Adrianol (Адрианол); *Spain*: Rhinospray Antialergico.

Tuaminoheptane Sulfate *(BANM, rINNM)* ⊗

Sulfato de tuaminoheptano; Tuaminoheptane, Sulfate de; Tuaminoheptane Sulphate; Tuaminoheptani Sulfas; Tuaminoheptano, sulfato de; Туаминогептана Сульфат.

$(C_7H_{17}N)_2H_2SO_4$=328.5

CAS — 6411-75-2.

ATC — R01AA11; R01AB08.

ATC Vet — QR01AA11; QR01AB08.

UNII — WZKSLN5CNW.

Profile

Tuaminoheptane is a volatile sympathomimetic (p. 1507.3) that has been used as the sulfate for the symptomatic relief of nasal congestion. Tuaminoheptane has also been used in the form of the carbonate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Rinofluimucil; *Fr.*: Rhinofluimucil; *Hong Kong*: Rinofluimucil†; *Hung.*: Rinofluimucil; *Ital.*: Rinofluimucil; *Port.*: Rinofluimucil; *Rus.*: Rinofluimucil (Ринофлуимуцил); *Spain*: Rinoflumil; *Switz.*: Rinofluimucil; *Thai.*: Rinofluimucil; *Ukr.*: Rinofluimucil (Ринофлуимуцил).

Tymazoline Hydrochloride *(BANM)* ⊗

2-Thymyloxymethyl-2-imidazoline Hydrochloride; Timazolina, hidrocloruro de; Tymazolini Hydrochloridum; Tymazoliny chlorowodorek; Тимазолина Гидрохлорид.

2-(2-Isopropyl-5-methylphenoxymethyl)-2-imidazoline hydrochloride.

$C_{14}H_{20}N_2O$,HCl=268.8

CAS — 24243-97-8 (tymazoline); 28120-03-8 (tymazoline hydrochloride).

ATC — R01AA13.

ATC Vet — QR01AA13.

Pharmacopoeias. In *Pol.*

Profile

Tymazoline is a sympathomimetic that has been used as the hydrochloride similarly to naphazoline (p. 1669.3) for its local vasoconstrictor effect in the symptomatic relief of nasal congestion.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Thymazen†; *Thal.*: Permazene†.

Xylometazoline Hydrochloride

(BANM, rINNM) ⊗

Hidrocloruro de xilometazolina; Ksilometazolin Hidroklorür; Ksilometazolino hidrochloridas; Ksylometatsoliinihydroklori; Ksylometazoliny chlorowodorek; Xilometazolina, hidrocloruro de; Xilometazolinhidroklorid; Xylométazoline, chlorhydrate de; Xylometazolinhydro; Xylometazolinhydrochlorid; Xylometazolinhydrochlorid; Xylometazolini Hydrochloridum; Ксилометазолина Гидрохлорид.

2-(4-*tert*-Butyl-2,6-dimethylbenzyl)-2-imidazoline hydrochloride.

$C_{16}H_{24}N_2HCl$=280.8

CAS — 526-36-3 (xylometazoline); 1218-35-5 (xylometazoline hydrochloride).

ATC — R01AA07; R01AB06; S01GA03.

ATC Vet — QR01AA07; QR01AB06; QS01GA03.

UNII — X5S84033NZ.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Xylometazoline Hydrochloride). A white or almost white, crystalline powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

USP 36: (Xylometazoline Hydrochloride). A white to off-white, odourless, crystalline powder. Soluble 1 in 35 of water; freely soluble in alcohol; sparingly soluble in chloroform; practically insoluble in ether and in benzene. pH of a 5% solution in water is between 5.0 and 6.6. Store in airtight containers. Protect from light.

Uses and Administration

Xylometazoline is a direct-acting sympathomimetic (p. 1507.3) with marked alpha-adrenergic activity. It is a vasoconstrictor which reduces swelling and congestion when applied to mucous membranes. The effect begins within 5 to 10 minutes of application and lasts for up to 10 hours.

Xylometazoline is used as the hydrochloride for the short-term symptomatic relief of nasal congestion (p. 1652.1). A 0.1% solution of xylometazoline hydrochloride is applied topically as nasal drops or a spray into each nostril two or three times daily. For doses in children, see below.

Xylometazoline hydrochloride solution is instilled into the eye as a conjunctival decongestant (see Conjunctivitis, p. 611.1). Preparations containing 0.05% xylometazoline hydrochloride with 0.5% antazoline sulfate are typical; 0.1% xylometazoline hydrochloride has also been used.

Administration in children. Over-the-counter cough and cold preparations containing sympathomimetic decongestants (including xylometazoline) should be used with caution in children and generally avoided in young children, for details see Cough, p. 1651.2. The *BNFC* suggests that xylometazoline nasal drops may be used in children aged 6 to 12 years for the short-term treatment of severe nasal congestion which has not responded to sodium chloride nasal drops or inhalation of warm moist air. A 0.05% solution of xylometazoline hydrochloride is licensed for such use; 1 or 2 drops are instilled into each nostril once or twice daily, for a maximum of 5 days.

Adverse Effects, Treatment, and Precautions

As for Naphazoline, p. 1669.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies xylometazoline for nasal use as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 27/10/11)

Interactions

Since xylometazoline is absorbed through the mucosa interactions may follow topical application. The *BNF* considers that all sympathomimetic nasal decongestants may cause a hypertensive crisis if used during treatment with an MAOI. For the interactions of sympathomimetics in general, see p. 1508.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Nastizol; Otrivina; *Austral.*: Otrivin; *Austria*: Otrivin; RatioSoft; Xylo-COMOD; *Belg.*: Nasa Rhinathiol; Nasasinutab; Nuso-San; Otrivine Anti-Rhinitis; *Braz.*: Otrivina; *Canad.*: Balminil Decongest; Balminil Nasal Decongestant; Certified Decongestant†; Cold and Allergy Decongestant†; Decongest; Decongestant Nasal Spray; Decongestant Nose Drops; Nasal Decongestant; Otrivin; Vaporisateur Nasal Decongestionnant; *China*: TianCheng Nuo Er (天诚诺尔); *Cz.*: Mar Rhino; Nasenspray AL; Nasentropfen AL†; Olynth; Otrivin; Rhino-Stas; Rinoxyl; Snup; Xylo-COMOD; Xylorin; *Denm.*: Klarigen; Noxorin; Otrivin; Passagen†; Zymelin; *Fin.*: Naso-Ratiopharm; Nasolin; Otrivin; *Ger.*: Balkis†; Gelonasal; Hysan Schnupfenspray; Nasaltropfen axcount†; Nasengel AL; Nasengel; Nasenspray AL†; Nasenspray E†; Nasenspray K†; Nasenspray; Nasentropfen AL†; Nasentropfen Stada†; Nasentropfen-ratiopharm; Olynth; Otriven gegen Schnupfen†; Otriven†; Rapako xylo; schnupfen endrine; Siozwo; Snup; Tussamag Nasenspray†; Xylo-COMOD†; Xylo-POS†; *Gr.*: Otrivin-Menthol; Otrivin; Silphin; *Hong Kong*: Decongestant Nasal Spray; Otrivin; Xyloma; *Hung.*: Nasan; Novorin; Otrivin; Rhinathiol; Rhino-Stas†; *India*: Acolate DPS; Atrovin; Biomist; Birvine; Broflex; Caxyl; Cyfer; Decon; Diconal; Goair; Hynasal-XL; Loxzol; Mucoris; Nam Cold Nasal; Naso Wikoryl; Nasomet; Nasrea; Nazalin†; Nazle; Nazolin; Nomocon; Nos-Air; Nozin; Nozy; Opun; Ortinase; Ortinose; Otrinoz; Otrivin; *Indon.*: Otrivin; *Irl.*: Otrivine; Sudafed Non-Drowsy Decongestant; *Israel*: Al-Care; Nazalet; Otrivin; Xylo-POS; Xylovit; *Ital.*: Argotone Dec; Neo Rinoleina; Otrivin; *Malaysia*: Otrivin; *Neth.*: Kruidvat Neusdruppels†; Meralys; Mucorhinyl; Nasadur; Nasomaris; Nasonal; Otrivin; Xyladur; Xylo-COMOD†; Xylo-POS; Xylozolin; *Norw.*: Naso; Nazaren; Otrivin; Xolin†; Zymelin; *NZ*: Otrivine; *Philipp.*: Otrivin; *Pol.*: Otrivin; Xylogel; Xylorin; *Port.*: Otrivina; Rinorex†; *Rus.*: Dlianos (Длянос); Grippostad Rhino (Гриппостад Рино); Halazolin (Галазолин); Influrin (Инфлюрин); Olynth (Олинт)†; Otrivin (Отривин); Pharmazolin (Фармазолин); Rhinonorm (Риноворм); Rhinorus (Ринорус); Rhinostop (Риностоп); Snup (Снуп); Suprima-Nos (Суприма-Нос); Tyzine Xylo (Тизин Ксило); Xilen (Ксилен); Xymelin (Ксимелин); *S.Afr.*: Otrivin; Sinutab; *Singapore*: Otrivin; *Spain*: Amidrin; Frenasal; Idasal; Otrivin†; Rhinovin; Rinoblanco; *Swed.*: Nasoferm; Olynth; Otrivin; *Switz.*: Nasben†; Nasobol Xylo; Olynth†; Otrivin; Rhinostop; Rinosedin; Spray nasal neo; Xylo-Mepha; *Thai.*: Otrivin; *Turk.*: Berkolin; Naze; Otrivine; Rinizol; Xylo-COMOD; *UAE*: Xylolin; *UK*: Non-Drowsy Sudafed Decongestant Nasal Spray; Otradrops; Otraspray; Otrivine; Tixycolds Cold and Allergy†; *Ukr.*: Dr Theiss Nasal Spray (Спрей Назальный Др Тайсс)†; Eucazolin (Эвказолин); Galazolin (Галазолин); Meralys (Мералис); Otrivin (Отривин); Rinazal (Риназал); Tyzine Xylo (Тизин Ксило); Xylo-Mepha (Ксило-Мефа); Xylohexal (Ксилогексал)†; *USA*: 4-Way Moisturizing Relief; Otrivin.

Multi-ingredient Preparations. *Austral.*: Murine Allergy; *Austria*: Nasic; *Belg.*: Otrivine Duo; *Chile*: Bacitopic Compuesto†; Nasomin; Rinobanedif; *Cz.*: Nasic; *Denm.*: Otrivin Menthol; Zymelin Plus; *Fin.*: Otrivin Comp; Otrivin Menthol; *Ger.*: Nasic; *Gr.*: Nasosyn; Otrivin Advance; *Hung.*: Otrivin Duo; *Irl.*: Otrivine Antistin; *Israel*: Otrivin Complete; *Ital.*: Inalar; *Mex.*: Rinade Compuesto; *Neth.*: Otrivin Duo; Otrivin Menthol; *Norw.*: Otrivin Comp; Otrivin med mentol; Zycomb; *NZ*: Otrivine-Menthol; Otrivine-Antistin†; *Pol.*: Otrivin Duo; *Port.*: Otrifar *Rus.*: Xymelin Extra (Ксимелин Экстра); *Spain*: Otriduo; *Swed.* Otrivin Comp; Otrivin Menthol; ZyComb†; *Switz.*: Nasic; Trio fan Rhume; *Turk.*: Otrivine Mentol; Rynacrom Compound *UK*: Otrivine-Antistin; *Ukr.*: Xymelin Extra (Ксимелин Экстра) Zycomb (Зикомб)†.

Pharmacopoeial Preparations

BP 2014: Xylometazoline Nasal Drops;

USP 36: Xylometazoline Hydrochloride Nasal Solution.

Zipeprol Hydrochloride *(rINNM)*

CERM-3024; Hidrocloruro de zipeprol; Zipéprol, Chlorhydrate de; Zipeprol, hidrocloruro de; Zipeproli Hydrochloridum; Зипепрола Гидрохлорид.

α-(α-Methoxybenzyl)-4-(β-methoxyphenethyl)-1-piperazineethanol dihydrochloride.

$C_{23}H_{32}N_2O_3.2HCl$=457.4

CAS — 34758-83-3 (zipeprol); 34758-84-4 (zipeprol hydrochloride).

ATC — R05DB15.

ATC Vet — QR05DB15.

UNII — U6WT9D8ASL.

Profile

Zipeprol is a centrally acting cough suppressant that is stated to have a peripheral action on bronchial spasm. It has been given as the hydrochloride in the treatment of cough (p. 1651.2), typically in an oral dose of 150 to 300 mg daily in divided doses. There have been reports of abuse and overdosage producing neurological symptoms.

Abuse and overdosage. Severe neurological symptoms have been reported in young adults after habitual abuse of zipeprol for euphoria. Patients have presented with generalised seizures, followed by coma.[1] One patient who ingested 750 mg of zipeprol [over twice the maximum daily dose] had several opisthotonic crises and developed cerebral oedema.[2] Symptoms of overdosage in children have included restlessness, somnolence, ataxia, choreic movements, forced deviation of the head and eyes, generalised seizures, respiratory depression, and coma.[1,3] Fatalities have been reported.

Dependence and withdrawal symptoms similar to those produced by opioids have been reported.[4] WHO has assessed zipeprol to have a moderate potential for dependence and liability for abuse.[5] Although zipeprol is a weak opioic agonist at high doses its toxicity and hallucinogenic and other psychotropic effects constitute a significant element in its abuse, and the public health and social problems associated with such abuse were considered substantial.

1. Moroni C, *et al.* Overdosage of zipeprol, a non-opioid antitussive agent. *Lancet* 1984; i: 45.
2. Perraro F, Beorchia A. Convulsions and cerebral oedema associated with zipeprol abuse. *Lancet* 1984; i: 45–6.
3. Merigot P, *et al.* Les convulsions avec trois antitussifs dérivés substitués dé la pipérazine (zipéprol, éprazinone, éprozinol). *Ann Pediatr (Paris)* 1985; 32: 504–11.
4. Mallaret MP, *et al.* Zipeprol: primary dependence in an unaddicted patient. *Ann Pharmacother* 1995; 29: 540.
5. WHO. WHO expert committee on drug dependence: twenty-ninth report. *WHO Tech Rep Ser 856* 1995. Also available at: http://whqlibdoc.who.int/trs/WHO_TRS_856.pdf (accessed 11/05/07)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Prenotos; *Gr.*: Delaviral; Demetovix; Devixil; Dovavixin; Duo-Extolen; Jactuss; Sousibim; *Mex.*: Tusigen.

Multi-ingredient Preparations. *Gr.*: Extolen.

Dermatological Drugs and Sunscreens

The skin is subject to a very wide range of lesions. Some may be characteristic of specific systemic diseases and fade as the disease regresses. Some are caused by specific local infections and are best treated by the appropriate antimicrobial (see Skin Infections in the chapters Antibacterials, p. 207.1, and Antifungals, p. 568.1). The skin is also subject to damage from environmental hazards. Excessive or prolonged exposure to solar radiation is associated with degenerative changes in the skin (premature ageing of the skin or photoageing; p. 1686.2), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), and malignant neoplasms of the skin (p. 714.1). Some skin disorders are adverse effects of therapeutic and other agents, ranging from mild hypersensitivity to the life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis (see Drug-induced Skin Reactions, p. 1683.3, and Drug-induced Photosensitivity, p. 1686.1). There also remain skin disorders whose aetiology is poorly understood.

The distribution and morphological description of the skin lesion (its shape, colour, and surface characteristics) are important in the diagnosis of skin disorders. There are many terms used to describe skin lesions:

- abscess–a collection of pus in a cavity
- bulla (or blister)–a fluid-filled circumscribed lesion larger than 0.5 cm in diameter
- comedo–a plug of keratin and sebum in a pilosebaceous follicle
- ecchymosis (bruise)–an extravasation of blood into the skin
- erythema–red coloration due to vascular dilatation
- fissure–a slit through the whole thickness of the skin
- horn–a thickening of the skin that is taller than it is broad
- keratosis–a horny thickening of the skin
- lichenification–hard, thickened skin with increased markings
- macule–an area of altered colour or texture with no elevation above the surface of the surrounding skin
- nodule–a dome-shaped or spherical-shaped, solid lesion, usually more than 0.5 cm in diameter and depth
- papilloma–a nipple-like mass
- papule–a raised solid lesion, usually less than 0.5 cm in diameter
- petechia–a pinhead-sized macule of blood in the skin
- plaque–a raised, flat-topped, circumscribed lesion, usually larger than 2 cm in diameter but with no substantial depth
- purpura–a macule of blood in the skin, larger than a petechia
- pustule–an accumulation of pus in the skin
- scale–a flat plate or flake of stratum corneum
- stria–a streak-like, linear, atrophic lesion, pink, purple, or white in colour
- telangiectasia–a visible permanent dilatation of small cutaneous blood vessels
- ulcer–a loss of the whole thickness of dermis and epidermis produced by sloughing of necrotic tissue; healing results in a scar
- vesicle–a fluid-filled circumscribed lesion less than 0.5 cm in diameter
- wheal–an elevated, white, compressible area of oedema often surrounded by a red flare

Dermatological Drug Groups

Treatment of skin disorders may include topical and/or systemic drug therapy, although the pharmacology of many of the drugs used in dermatology is poorly understood. Physical methods such as cryotherapy, UV radiation, radiotherapy, and surgery also have a role. Some of the main drug groups used in dermatology are described below.

Antidandruff Drugs

Antidandruff drugs have antibacterial and antifungal properties and are used particularly in shampoos to manage dandruff and seborrhoeic dermatitis of the scalp.

Described in this chapter are
- Dipyrithione, p. 1701.1
- Piroctone Olamine, p. 1716.3
- Pyrithione Zinc, p. 1718.1
- Selenium Sulfide, p. 1719.3
- Tars and Tar Oils, p. 1723.2

Corticosteroids

Corticosteroids are widely used for their anti-inflammatory (glucocorticoid) and immunosuppressant properties in the management of various skin conditions. Topical preparations are commonly used, but systemic treatment may be required for severe conditions or to control acute exacerbations. The actions and uses of the corticosteroids are discussed in much greater detail in the section beginning on p. 1597.1. See also below for other immunosuppressants used in dermatology.

Immune System Modifiers

Some immunosuppressants are used specifically in psoriasis or eczema, and are included in this chapter. Other immunosuppressants and antineoplastics with immunosuppressant properties that are used in dermatology and covered in other chapters include azathioprine (p. 1940.3), ciclosporin (p. 1945.2), methotrexate (p. 822.2), and tacrolimus (p. 1968.3). Corticosteroids are also widely used for their anti-inflammatory and immunosuppressant effects (see above). Adalimumab (p. 17.2), etanercept (p. 55.1), and infliximab (p. 74.2) are immunomodulators also used in the management of psoriasis.

Described in this chapter are
- Alefacept, p. 1692.3
- Efalizumab, p. 1702.2
- Pimecrolimus, p. 1716.1
- Ustekinumab, p. 1728.2

Keratolytics

Keratolytics help to soften and ease exfoliation of the horny layer of the epidermis, and are used in conditions such as acne, seborrhoeic dermatitis and dandruff, and hyperkeratotic disorders.

Described in this chapter are
- Aldioxa, p. 1692.2
- Aldioxa, p. 1692.2
- Allantoin, p. 1693.1
- Benzoyl Peroxide, p. 1696.1
- Glycolic Acid, p. 1704.3
- Keluamid, p. 1710.2
- Resorcinol, p. 1718.3
- Salicylic Acid, p. 1719.1
- Salnacedin, p. 1719.3
- Sulfur, p. 1721.1
- Tioxolone, p. 1725.1
- Urea, p. 1727.3

Photosensitisers

Psoralen photosensitisers markedly increase the skin's sensitivity to UVA light, and are used in photochemotherapy (PUVA) for the management of disorders such as psoriasis, vitiligo, cutaneous T-cell lymphoma, and polymorphic light eruption. For a discussion of photodynamic therapy, a form of light-activated treatment used in the management of malignant neoplasms, see under Porfimer Sodium, p. 849.1.

Described in this chapter are
- Methoxsalen, p. 1711.3
- 5-Methoxypsoralen, p. 1714.1
- Trioxysalen, p. 1727.2

Pigment Modifiers

Drugs such as hydroquinone that reduce pigmentation are used to lighten skin in hyperpigmentation conditions such as chloasma. Dihydroxyacetone is used to darken skin in vitiligo, and monobenzone is used to permanently depigment normal skin in extensive vitiligo. Erythrulose is used to darken skin, either alone or with dihydroxyacetone, in artificial suntan preparations. Photosensitisers (above) are also used in vitiligo.

Described in this chapter are
- Arbutin, p. 1694.3
- Azelaic Acid, p. 1695.1
- Dihydroxyacetone, p. 1700.1
- Erythrulose, p. 1703.3
- Glycolic Acid, p. 1704.3
- Hydroquinone, p. 1705.1
- Kojic Acid, p. 1710.2
- Mequinol, p. 1711.1
- Monobenzone, p. 1714.2

Retinoids

Retinoids, and the retinoid analogue adapalene, are vitamin A analogues used in the management of various skin conditions including acne, psoriasis, and keratinisation disorders. Liarozole (p. 1710.3) increases retinoic acid concentrations in the body, and is under investigation for various skin disorders.

Described in this chapter are
- Acitretin, p. 1690.3
- Adapalene, p. 1692.1
- Etretinate, p. 1703.3
- Isotretinoin, p. 1706.2
- Motretinide, p. 1714.3
- Retinaldehyde, p. 1719.1
- Tazarotene, p. 1724.2
- Tretinoin, p. 1725.2

Sunscreens

Sunscreens are used to protect the skin against sunlight. There are 2 types: *physical* (reflective or inorganic) agents that are opaque and reflect both UVA and UVB radiation and *chemical* (absorbent or organic) agents that because of their chromophore groups absorb a particular range of wavelengths within the UV spectrum (for definitions, see Light-induced Skin Reactions, p. 1685.3). Physical sunscreens include titanium dioxide and zinc oxide. A classification of the chemical sunscreens included in this chapter is given in Table 1, below. Many products combine sunscreens from different groups in order to widen the protection afforded.

Table 1. Chemical sunscreens.

UVA absorbers	UVB absorbers
Anthranilates	**Aminobenzoates**
Meradimate	Aminobenzoic acid
Camphorsulfonic acid derivatives	Lisadimate
Ecamsule	Padimate
Dibenzoylmethanes	Padimate O
Avobenzone	**Camphor derivatives**
Dibenzoylmethane	Enzacamene
Isopropyldibenzoylmethane	**Cinnamates**
UVA and UVB absorbers	Amiloxate
Benzophenones	Cinoxate
Dioxybenzone	Diolamine methoxycinnamate
Mexenone	Octinoxate
Oxybenzone	Octocrilene
Sulisobenzone	**Salicylates**
	Homosalate
	Octisalate

Trolamine salicylate (p. 141.2) and salol (p. 129.3) are salicylic acid derivatives that have analgesic properties, but have also been used as sunscreens.

Described in this chapter are

Amiloxate, p. 1694.1
Aminobenzoic Acid, p. 1694.2
Avobenzone, p. 1695.1
Bemotrizinol, p. 1695.3
Bisoctrizole, p. 1697.1
Cinnamates, p. 1699.2
Cinoxate, p. 1699.2
Dibenzoylmethane, p. 1700.1
Diolamine Methoxycinnamate, p. 1700.2
Dioxybenzone, p. 1700.2
Drometrizole, p. 1702.1
Ecamsule, p. 1702.1
Ensulizole, p. 1703.1
Enzacamene, p. 1703.2
Homosalate, p. 1705.1
Iscotrizinol, p. 1706.1
Isopropyldibenzoylmethane, p. 1706.2
Lisadimate, p. 1710.3
Melanin, p. 1711.1
Meradimate, p. 1711.2
Methyl Anthranilate, p. 1714.2
Mexenone, p. 1714.2
Octil Triazone, p. 1715.1
Octinoxate, p. 1715.1
Octisalate, p. 1715.2
Octocrilene, p. 1715.2
Oxybenzone, p. 1715.3
Padimate, p. 1715.3
Padimate O, p. 1716.1
Sulisobenzone, p. 1722.1
Titanium Dioxide, p. 1725.1
Zinc Oxide, p. 1729.1

Vitamin D Derivatives

Some vitamin D derivatives are used in the treatment of psoriasis because they appear to induce differentiation and suppress proliferation of keratinocytes. Mention of other vitamin D derivatives that have been studied in psoriasis can be found under Vitamin D Substances, p. 2112.3.

Described in this chapter are

Calcipotriol, p. 1697.2
Tacalcitol, p. 1722.1

Wound Management Agents

Many compounds and dressings are used in the management of wounds and ulcers. Although some are included in this chapter, others can be found throughout *Martindale*, including white and yellow soft paraffins (p. 2211.3), alginates such as calcium alginate (p. 1136.3), proteolytic enzymes such as collagenase (p. 2484.1) and fibrinolysin (p. 1382.3), and fibrin glue (p. 1151.2).

Described in this chapter are

Becaplermin, p. 1695.2
Centella, p. 1698.3
Cerous Nitrate, p. 1699.1
Crilanomer, p. 1699.2
Dextranomer, p. 1699.3
Maggots, p. 1711.1
Polyphloroglucinol Phosphate, p. 1717.3
Polyurethane Foam, p. 1718.1
Prezatide Copper Acetate, p. 1718.1
Pyroxylin, p. 1718.2
Skin Substitutes, p. 1720.2
Trafermin, p. 1725.1

Topical Drug Administration

For drugs that are applied topically, the vehicle and formulation may be as important as the active drug. Indeed, some cream and ointment bases are used alone for their protective or emollient properties, while adverse effects of topical preparations are sometimes attributed to constituents of the vehicle such as stabilisers and preservatives. The choice of formulation depends on the skin condition being treated and the area affected. Lotions and gels are useful for hairy areas. Creams (oil-in-water emulsions) have cooling and emollient effects, are readily absorbed by the skin, and are used for acute and exudative conditions. Ointments (water-in-oil emulsions) are more occlusive than creams and are particularly suitable for dry lesions. Pastes (powder incorporated in an ointment basis) are also occlusive and are useful for their protective properties and for their use on circumscribed lesions. Less frequently used formulations include applications, collodions, and dusting powders. Typical quantities of preparations required per week for twice daily application to specific areas of an adult are given in Table 2, below.

Table 2. Typical quantities of preparations required per week for twice daily application to an adult.

	Creams and Ointments	Lotions
Face	15 to 30 g	100 mL
Both hands	25 to 50 g	200 mL
Scalp	50 to 100 g	200 mL
Both arms or both legs	100 to 200 g	200 mL
Trunk	400 g	500 mL
Groins and genitalia	15 to 25 g	100 mL

NOTE. These quantities do *not* apply to corticosteroid preparations.

Management of Dermatological Disorders

The management of some of the commoner skin conditions is discussed below.

Acne

Acne is a disorder of the pilosebaceous follicle; common features include increased sebum production, follicular keratinisation, colonisation by *Propionibacterium acnes*, and localised inflammation. Mild acne is characterised by open or closed comedones (blackheads and whiteheads), some of the latter developing into inflamed lesions such as papules and pustules. In moderate acne, the papules and pustules are more widespread, and there may be mild scarring. Severe acne is characterised by the presence of nodular abscesses or cysts in addition to widespread pustules and papules, and may lead to extensive scarring.

The most common form of acne is acne vulgaris. It is common in teenagers and while by their mid-20s the majority of cases have resolved, a few people still require treatment in their 30s and 40s. Skin areas typically affected are the face, shoulders, upper chest, and back. Acne may also occur in late middle age and in the elderly (late onset acne) and in infants (infantile acne). Certain drugs, including androgens, corticosteroids, corticotropin, hormonal contraceptives containing androgenic progestogens such as levonorgestrel, isoniazid, lithium, methoxsalen, and some antiepileptics may produce an acneform rash, as may substances such as tars, oils, and oily cosmetics.

Treatment aims to reduce the bacterial population of the pilosebaceous follicles, reduce the rate of sebum production, reduce inflammation, and remove the keratinised layer blocking the follicles. Drugs used include keratolytics, retinoids, and antibacterials. If topical preparations are not effective, oral preparations may be required. Response to therapy is commonly slow and long-term treatment is usually necessary.

Mild acne is treated topically, in particular with benzoyl peroxide, retinoids, and antibacterials. Abrasives have been used but their efficacy is doubtful, and preparations based on sulfur or salicylic acid are considered by some to be obsolete; irritating astringents, harsh cleansers, and antibacterial soaps should be avoided. Topical corticosteroids, despite their presence in some compound preparations, should not be used.

Benzoyl peroxide has an antimicrobial action and mild keratolytic properties, and both comedones and inflammation generally respond well. It is probably the most widely used drug in mild acne because of its ready availability. Azelaic acid is an alternative to benzoyl peroxide that may cause less local irritation, but be less effective. Topical retinoids are effective in both comedonal and inflammatory acne; tretinoin is widely used but isotretinoin and tazarotene are considered to be equally effective. Adapalene, a naphthoic acid derivative with retinoid activity, also has similar efficacy, but may be better tolerated. Topical antibacterials can be used particularly for inflammatory acne. Tetracycline, clindamycin, and erythromycin are generally used, and appear to be roughly equivalent in efficacy. However, development of resistance by the skin flora is an increasing problem. Nicotinamide has also been used topically in mild to moderate inflammatory acne.

Generally, benzoyl peroxide is used alone as a first-line therapy for mild inflammatory acne, and topical retinoids can be used when comedones predominate.[1,2] Topical antibacterials may be used in inflammatory acne but should not be used alone; the addition of a topical retinoid or benzoyl peroxide improves efficacy and reduces the risk of developing resistance. However, many patients have both comedonal and inflammatory acne to some degree, and a retinoid with benzoyl peroxide, or a retinoid with benzoyl peroxide and a topical antibacterial, can be used.[3] Once there is clinical improvement and inflammatory lesions are under control, which may take 8 to 12 weeks,[4] the antibacterial can be stopped and the retinoid continued as maintenance therapy.[3] If there is no improvement within 6 to 8 weeks with antibacterial therapy, treatment should be stopped.[5] Further courses of topical antibacterial may be needed for flare-ups.[3]

Moderate acne is best treated with oral rather than topical antibacterials, of which tetracyclines appear to be the drugs of first choice. Tetracycline, doxycycline, lymecycline, or oxytetracycline may be used. Minocycline has also been reported to be effective; however, it can cause skin pigmentation and may be associated rarely with immunologically mediated reactions. Alternatives to the tetracyclines include erythromycin, co-trimoxazole, and trimethoprim. Resistance is an important problem, especially with erythromycin, and benzoyl peroxide is therefore also used.[3,6] To further limit the development of resistance, antibacterials should be used for no longer than necessary, the same antibacterial should be used for subsequent courses if the patient relapses,[3,6] and oral and topical antibacterials should not be used together.[6] Oral antibacterials have to be used for at least 3 months.[3,6] A total course of up to 6 months may be needed; longer treatment should generally be avoided but may be warranted in some cases.[6] If there is no response after 6 to 8 weeks, the antibacterial should be changed.[3] A topical retinoid may also be used for additional comedolytic activity. After the course of antibacterial has finished, a topical retinoid alone or with benzoyl peroxide is continued as maintenance therapy.[3] Women with moderate acne who also require oral contraception may be treated additionally with a combined oral contraceptive containing a non-androgenic progestogen.[2,4]

Severe acne is usually treated with oral isotretinoin; there are also reports of oral isotretinoin being used outside this licensed indication for less severe acne that is resistant to treatment or that is causing physical scarring or psychological distress.[1] Where it cannot be used, high dose of oral antibacterials with a topical retinoid and benzoyl peroxide may be considered.[6] In women with signs of hyperandrogenism,[2-4] adjunctive use of the combination of anti-androgenic cyproterone with ethinylestradiol may be considered (this is available as a combination preparation that also provides contraception). A combined (non-androgenic) contraceptive is an alternative. Spironolactone has been used for its anti-androgenic properties in women when oestrogens are contra-indicated.

There is evidence to suggest that photodynamic therapy with a photosensitiser, such as 5-aminolevulinic acid, may be beneficial in acne.[7-9]

1. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Pediatr Drugs* 2003; 5: 301–13.
2. James WD. Acne. *N Engl J Med* 2005; 352: 1463–72.
3. Zaenglein AL, Thiboutot DM. Expert committee recommendations for acne management. *Pediatrics* 2006; 118: 1188–99. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/3/1188.pdf (accessed 25/09/07)
4. Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA* 2004; 292: 726–35.
5. Dreno B. Topical antibacterial therapy for acne vulgaris. *Drugs* 2004; 64 2389–97.
6. Dréno B, *et al.* European recommendations on the use of oral antibiotics for acne. *Eur J Dermatol* 2004; 14: 391–9. Also available at: http://www.john-libbey-eurotext.fr/en/revues/medecine/ejd/e-docs/00/04/07/1B/article.phtml (accessed 08/07/10)
7. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; 159: 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 25/05/10)
8. Taylor MN, Gonzalez ML. The practicalities of photodynamic therapy in acne vulgaris. *Br J Dermatol* 2009; 160: 1140–8.
9. Hamilton FL, *et al.* Laser and other light therapies for the treatment of acne vulgaris: systematic review. *Br J Dermatol* 2009; 160: 1273–85.

Alopecia

Alopecia (hair loss) has many causes but androgenetic alopecia is the most common form. Alopecia may also be congenital, be associated with systemic disorders, severe emotional and physical stress, or skin disorders, or be due to nutritional deficiencies. Some drugs may cause alopecia; examples include antineoplastics (see p. 730.3), beta blockers, diazoxide, heparin, verapamil, and warfarin. In cicatricial alopecia there is destruction of the hair follicles (scarring) resulting in permanent hair loss. Drug treatment may be tried in alopecia areata and androgenetic alopecia but it is often unsuccessful or has only a modest effect. Treatment of any other associated underlying condition causing alopecia, or removal of a suspected drug, may produce hair regrowth. Some treatments have also been tried in cicatricial alopecia in an attempt to stop the scarring process and permanent hair loss. Non-drug options include the use of wigs and hairpieces, cosmetic hair products, or hair transplantation surgery.

Alopecia areata is an auto-immune disorder in which there is a loss of hair in sharply defined areas of skin that normally bear hair. The affected area can vary in size from about 1 cm^2 to the whole scalp (alopecia totalis) or all body hair (alopecia universalis).

Small or isolated patches of alopecia areata may not need treatment and in many patients hair regrows within a few months. If loss of hair becomes a problem cosmetically, treatment may be offered but is often not totally satisfactory. Several treatment options have been tried.[1-3] Intralesional corticosteroids stimulate hair regrowth at the site of injection and may be of benefit for limited patchy hair loss. Oral pulsed or continuous corticosteroids may be used in severe progressive cases. Potent topical corticosteroids, topical dithranol, and minoxidil lotion may also be used, although their efficacy is debatable. Contact immunotherapy with diphencyprone has shown benefit in patients with extensive patchy hair loss, alopecia totalis and universalis. Photochemotherapy with ultraviolet A radiation (PUVA) with either systemic or topical psoralens such as methoxsalen has been tried, but potentially serious adverse effects and limited efficacy restrict its use.

Androgenetic alopecia is hereditary thinning of the hair induced by androgens in genetically susceptible men and women.[1] Over time, the growth phase of the hair cycle becomes shorter and hair follicles become smaller, producing shorter, finer hairs that cover the scalp poorly. *Male-pattern alopecia* (male-pattern baldness)[1,3,4] involves recession of the hairline in the frontal region of the scalp or

loss of hair at the vertex. It is usually associated with increasing age in men. Topical minoxidil is more effective in male-pattern alopecia than it is in the areata forms of alopecia, but is still, at best, only modestly effective. Because of the role of androgens in this condition anti-androgens and 5α-reductase inhibitors may also be tried. The 5α-reductase inhibitor finasteride has been shown to be of benefit in men with male-pattern alopecia. Alfatradiol, another 5α-reductase inhibitor, is available in some countries for topical use. To maintain effectiveness, minoxidil or finasteride must be used continuously as any benefit will be lost within months of stopping treatment. Androgenetic alopecia also occurs in women (*female-pattern alopecia*);[5] there is a similar pattern of hair loss although the thinning may be more diffuse and milder in women than men. Most women with androgenetic alopecia do not have elevated androgen concentrations and are treated with topical minoxidil. However, an anti-androgen such as cyproterone acetate or spironolactone might be considered for women with accompanying signs of hyperandrogenism such as hirsutism (p. 2262.1). Finasteride and dutasteride are also being investigated in women with alopecia.[6]

Cicatricial alopecia involves inflammation and replacement of the hair follicles by fibrous tissue and the aim of treatment is to stop this process before hair loss is permanent. As well as hair loss, there can be pustules, crusting, scaling, and itching. There are several different types of cicatricial alopecia and many treatments have been tried, but there is no standard therapy.[7-9] In those where the scalp biopsy shows mainly lymphocytic infiltration, topical and/or intralesional corticosteroids can be used alone for limited disease or added to systemic therapy. Systemic corticosteroids may be used and other oral treatments that have been tried for more extensive or progressive disease include hydroxychloroquine, isotretinoin, mycophenolate mofetil, and ciclospòrin. There are also reports of benefit from other topical therapies such as pimecrolimus, tacrolimus, and tazarotene. In neutrophilic cicatricial alopecia, oral antibacterials are used to control follicular infection and suppuration. Oral isotretinoin has been used in patients with neutrophilic dissecting cellulitis.

1. Price VH. Treatment of hair loss. *N Engl J Med* 1999; 341: 964–73.
2. MacDonald Hull SP, *et al.* British Association of Dermatologists. Guidelines for the management of alopecia areata. *Br J Dermatol* 2003; 149: 692–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Alopecia%20Areata.pdf (accessed 08/07/10)
3. Hordinsky MK. Medical treatment of noncicatricial alopecia. *Semin Cutan Med Surg* 2006; 25: 51–5.
4. Stough D, *et al.* Psychological effect, pathophysiology, and management of androgenetic alopecia in men. *Mayo Clin Proc* 2005; 80: 1316–22.
5. Shapiro J. Hair loss in women. *N Engl J Med* 2007; 357: 1620–30.
6. Camacho-Martínez FM. Hair loss in women. *Semin Cutan Med Surg* 2009; 28: 19–32.
7. Ross EK, *et al.* Update on primary cicatricial alopecias. *J Am Acad Dermatol* 2005; 53: 1–37.
8. Price VH. The medical treatment of cicatricial alopecia. *Semin Cutan Med Surg* 2006; 25: 56–9.
9. Harries MJ, *et al.* Management of primary cicatricial alopecias: options for treatment. *Br J Dermatol* 2008; 159: 1–22.

Burns

Burns may be caused by chemicals or heat. Initial treatment of burns is irrigation with cold or tepid water for at least 20 minutes; hypothermia should be avoided. This limits the skin damage in burns caused by heat and removes the causative agent in chemical burns. Sodium bicarbonate solution is then used on acid burns and acetic acid solution on alkaline burns. The extent of a burn injury is described by area and depth. The affected body-surface can be calculated, and the depth of the burn may be classified as superficial (first-degree); partial thickness (second-degree), which may be further classified as superficial or deep partial thickness; or full thickness (third-degree). The major problems associated with burns are hypovolaemic shock, inhalation injury, metabolic abnormalities, and infection. For burns affecting the eye, see p. 1782.1.

- After a burn, fluid accumulates rapidly in the wound area due to increased permeability of the microcirculation and this loss of fluid from the circulation may produce hypovolaemic shock (p. 1279.3) if burns involve at least 15 to 20% of the body-surface.
- Inhalation injury producing airway oedema is mainly a result of exposure to toxic gases. Endotracheal intubation is required until the oedema subsides. Oxygen therapy is used, and nebulised beta$_2$ agonists may be given to treat bronchospasm. Inhalation of heparin and acetylcysteine may be of benefit in reducing pulmonary failure.
- Hypermetabolism and marked catabolism can result from major burn injury. Protein breakdown and loss causes muscle wasting and weakness, impaired wound healing and skin breakdown, and impaired immunity. Other effects of metabolic disturbances include an increase in liver fat and hepatomegaly, osteopenia, tachycardia and increased myocardial oxygen consumption. Enteral feeding (p. 2044.1) to match nutrient requirements is essential for metabolic management. Other treatments that have been tried to reduce net catabolism include the amino acids arginine and glutamine, drugs with anabolic effects including insulin, oxandrolone, and somatropin (for concerns about the latter use see p. 1920.3), and catecholamine antagonism using beta blockers such as propranolol.
- Prevention of infection is an important part of burn wound management. Micro-organisms proliferate rapidly in burn wounds, especially those severe enough to impair immune function, and sepsis remains the major fatal complication of burns. Burn wounds should be cleansed with normal saline (see Wounds and Ulcers, p. 1690.1). This may be all that is required for very minor burn wounds; a non-adherent dressing, such as paraffin tulle, may be used if necessary. Topical antibacterials, such as chlorhexidine, sulfadiazine silver, silver nitrate, and mafenide acetate, may be applied as required. Sodium hypochlorite (Dakin's solution) may also be of value, although opinions differ as to its usefulness. Removal of devitalised tissue is also an essential element of management. Infections require aggressive systemic treatment (see under Skin Infections, p. 207.1).

Full thickness burn wounds require skin grafting. This is performed as soon as possible after stabilisation of the patient. Skin grafting may also be considered for deep partial thickness wounds. If the area to be grafted is very extensive, the grafting procedure may have to be in stages (at intervals of about a week) as sufficient autologous skin becomes available. Alternatively, temporary skin substitutes may be used to supplement autologous skin and allow wound closure in one stage. Cultured epidermal autografts may also be available to either supplement autologous skin, or to be used alone if necessary.

References.

1. Clarke J. Burns. *Br Med Bull* 1999; 55: 885–94.
2. Ramzy PI, *et al.* Thermal injury. *Crit Care Clin* 1999; 15: 333–52.
3. Demling RH, Seigne P. Metabolic management of patients with severe burns. *World J Surg* 2000; 24: 673–80.
4. Murphy KD, *et al.* Current pharmacotherapy for the treatment of severe burns. *Expert Opin Pharmacother* 2003; 4: 369–84.
5. Herndon DN, Tompkins RG. Support of the metabolic response to burn injury. *Lancet* 2004; 363: 1895–1902.
6. Hudspith J, Rayatt S. First aid and treatment of minor burns. *BMJ* 2004; 328: 1487–9.
7. Hettiaratchy S, Papini R. Initial management of a major burn: I—overview. *BMJ* 2004; 328: 1555–7.
8. Hettiaratchy S, Papini R. Initial management of a major burn: II—assessment and resuscitation. *BMJ* 2004; 329: 101–3.
9. Holland AJA. Pediatric burns: the forgotten trauma of childhood. *Can J Surg* 2006; 49: 272–7.
10. Benson A, *et al.* Burns. *BMJ* 2006; 332: 649–52. Correction. *ibid.*; 755.
11. Enoch S, *et al.* Emergency and early management of burns and scalds. Abridged version: *BMJ* 2009; 338: 937–41. Full version: http://www.bmj.com/cgi/content/full/338/apr08_1/b1037 (accessed 11/12/09)
12. Orgill DP. Excision and skin grafting of thermal burns. *N Engl J Med* 2009; 360: 893–901.

Darier's disease

Darier's disease (keratosis follicularis) is an uncommon inherited keratinisation disorder (see p. 1685.2) and is characterised by groups of horny papules over the body. These may become irritated and/or infected, exudative, and crusted. Involvement of the nails is characteristic. Severity varies greatly; emollients, use of soap substitutes, and wearing cool clothing are important in controlling irritation in all patients, and may be sufficient in the mildest cases. More severe cases are treated by topical application of keratolytics such as salicylic acid or topical retinoids such as isotretinoin, tretinoin, or tazarotene. Topical corticosteroids are helpful in some patients to alleviate retinoid-induced irritation. Treatment with oral retinoids (acitretin, etretinate, or isotretinoin) is needed in more extensive disease, and has been combined with topical retinoids. Ciclosporin and topical fluorouracil have also been tried; some patients have been reported to respond to dietary supplementation with essential fatty acids. There is only anecdotal evidence to support the use of surgery or laser therapy, although these may be tried in refractory cases.

References.

1. Burge S. Management of Darier's disease. *Clin Exp Dermatol* 1999; 24: 53–6.
2. Cooper SM, Burge SM. Darier's disease: epidemiology, pathophysiology, and management. *Am J Clin Dermatol* 2003; 4: 97–105.
3. Sehgal VN, Srivastava G. Darier's (Darier-White) disease/keratosis follicularis. *Int J Dermatol* 2005; 44: 184–92.

Dermatitis herpetiformis

Dermatitis herpetiformis is a rare blistering disorder of the subepidermal tissue in which the vesicles and papules are intensely irritant and pruritic. The knees, elbows, buttocks, shoulders, and scalp are areas typically affected. The disease presents usually during early to middle adult life and is a chronic condition, although there may be periods of remission that last several months. In most patients there is also a mild gastrointestinal absorptive defect characterised by gluten hypersensitivity (gluten enteropathy or coeliac disease, see p. 2043.1). Skin lesions can be suppressed by dapsone; the sulfonamides sulfamethoxypyridazine or sulfapyridine have been used as alternatives to dapsone.[1-6] A gluten-free diet may improve both gastrointestinal symptoms and the skin disorder.[2,4-7]

1. Pine J-D. Management of acquired bullous skin diseases. *N Engl J Med* 1995; 333: 1475–84.
2. Fry L. Dermatitis herpetiformis. *Baillieres Clin Gastroenterol* 1995; 9: 371–93.
3. Garioch JJ. Dermatitis herpetiformis and its management. *Prescribers' J* 1996; 36: 141–5.
4. Fry L. Dermatitis herpetiformis: problems, progress and prospects. *Eur J Dermatol* 2002; 12: 523–31.
5. Zone JJ. Skin manifestations of celiac disease. *Gastroenterology* 2005; 128 (suppl): S87–S91.
6. Caproni M, *et al.* Italian Group for Cutaneous Immunopathology. Guidelines for the diagnosis and treatment of dermatitis herpetiformis. *J Eur Acad Dermatol Venereol* 2009; 23: 633–8. Also available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/122254386/PDFSTART (accessed 24/05/10)
7. Garioch JJ, *et al.* 25 years' experience of a gluten-free diet in the treatment of dermatitis herpetiformis. *Br J Dermatol* 1994; 131: 541–5.

Drug-induced skin reactions

Drugs are a frequent cause of adverse skin reactions. The skin reaction may mimic a spontaneously occurring skin disorder and is therefore included in the differential diagnosis of most skin diseases. Alternatively, the drug may produce quite specific changes. The reaction can develop after the first dose or after a period of sensitisation. Pigmentation changes or effects on hair may take some months to become apparent. Drug-induced nail changes have also been reported.

Reactions range from mild rashes to severe life-threatening reactions including angioedema with urticaria, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Other serious skin reactions include hypersensitivity syndromes, serum sickness, and vasculitis.

Stevens-Johnson syndrome (see also Erythema Multiforme, p. 1684.3) is a severe, blistering skin reaction also affecting the mucous membranes of the oropharynx, eyes, and genitalia and accompanied sometimes by fever, pain, and malaise. **Toxic epidermal necrolysis** (Lyell's syndrome or scalded skin syndrome) as described on p. 1689.1, is a more severe form of the reaction where considerable amounts of the epidermis may be shed. Sulfonamides, carbamazepine, and allopurinol are among the many drugs that have been associated with both these reactions.

Hypersensitivity syndrome is a severe, idiosyncratic reaction which includes rash and fever, and often hepatitis, arthralgias, lymphadenopathy, and haematological abnormalities. It tends to have a relatively late and slow onset. Some antiepileptics and sulfonamides cause this syndrome, as well as allopurinol, dapsone, and gold salts. **Serum sickness** is manifest as rash, fever, arthralgia and arthritis and typically develops 8 to 14 days after doses of serum preparations and vaccines. **Vasculitic reactions** may occur 7 to 21 days after beginning therapy with drugs such as allopurinol, penicillins, and sulfonamides (see Hypersensitivity Vasculitis, p. 1606.1). The vasculitis usually affects small vessels of the lower extremities producing purpura, although it can also affect vessels in the kidney, liver, and gastrointestinal tract, in which case it may be life-threatening.

Maculopapular exanthematic eruptions are probably the most frequent drug-induced skin reaction. Drugs commonly causing these rashes include carbamazepine, chlorpromazine, nitrofurantoin, penicillins, and sulfonamides. **Urticaria** (p. 1689.2) is also frequently drug-induced. **Photosensitivity** rashes where the skin reaction is confined to light-exposed areas may be phototoxic or photoallergic in nature (see Drug-induced Photosensitivity, p. 1686.1). Amiodarone produces a phototoxic reaction in many patients. Some drugs cause **pigmentary changes** (see Pigmentation Disorders, p. 1687.2). Chlorpromazine can cause both photosensitivity and pigmentary changes. **Acneform eruptions** may be produced by many drugs (see Acne, p. 1682.2). Some drugs produce skin reactions resembling **pemphigus** and **pemphigoid** (see p. 1687.1). Most of the drugs implicated contain a thiol group or metabolism of the drug generates a thiol group. Examples include captopril, penicillamine, penicillins, piroxicam, and rifampicin. **Fixed-drug eruptions** are inflammatory patches that appear at the same sites each time the drug is taken, and may occur with many drugs including dapsone, sulfonamides, and tetracycline.

Drug-induced **nail changes** include onychomadesis, nail fragility, onycholysis, paronychia, pigmentation, and vascular changes. The effect is usually transient and disappears with drug withdrawal. Drugs reported to cause nail changes include antineoplastics, psoralens, retinoids, tetracyclines, and zidovudine.

The majority of drug-induced adverse skin reactions are mild. However, in severe reactions rapid withdrawal of the suspected drug is needed. In some cases, this may mean stopping several drugs. In most cases the skin reaction will be resolved by symptomatic treatment. Another dose of the offending drug may establish whether the skin eruption is

drug-induced, although reactions may be more severe and therefore rechallenge should not be performed after a serious reaction.

General references.
1. Smith AG. Important cutaneous adverse drug reactions. *Adverse Drug React Bull* 1994; 167: 631–4.
2. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994; 331: 1272–85.
3. Wolkenstein P, Revuz J. Drug-induced severe skin reactions: incidence, management and prevention. *Drug Safety* 1995; 13: 56–68.
4. Lee A, Thomson J. Drug-induced skin reactions. *Pharm J* 1999; 262: 357–62.
5. Piraccini BM, Tosti A. Drug-induced nail disorders: incidence, management and prognosis. *Drug Safety* 1999; 21: 187–201.
6. ten Holder SM, *et al.* Cutaneous and systemic manifestations of drug-induced vasculitis. *Ann Pharmacother* 2002; 36: 130–47.
7. Wolf R, *et al.* Life-threatening acute adverse cutaneous drug reactions. *Clin Dermatol* 2005; 23: 171–81.

Eczema

Eczema (often used synonymously with the term dermatitis) refers to a variety of skin conditions characterised by epidermal inflammation and itching. The areas of skin affected vary in the different types of eczema, but the skin lesions share certain common features. In acute eczema the skin is typically red and inflamed with papules, vesicles, and blisters. In chronic eczema the skin may show the same features but be more dry, scaly, pigmented, and thickened. Eczema may be categorised as exogenous (including allergic, irritant, and photosensitivity eczema) or endogenous (such as atopic, discoid/nummular, gravitational, and seborrhoeic eczema), but there may be multiple causes of eczema, both endogenous and exogenous, in an individual patient. Two of the most common forms of eczema are atopic eczema (see below) and seborrhoeic dermatitis (p. 1689.1).

Atopic eczema mainly affects infants and children although adults may also suffer. The skin is itchy and there is a chronic or relapsing dermatitis in which the face and neck and flexures of the elbows and knees are involved most often and are excoriated and lichenified.

General principles for the management of **atopic eczema** may also be applied to other eczematous skin disorders. Cure of atopic eczema is said to be unrealistic, but good control can be achieved with proper management. The objective of treatment should be to reduce signs and symptoms, to prevent or reduce recurrences, and to provide long-term management by preventing exacerbation. Guidelines have been issued by, among others, the Primary Care Dermatology Society with the British Association of Dermatologists,[1] the American Academy of Dermatology,[2] the International Consensus Conference on Atopic Dermatitis (ICCAD II),[3] and, in the UK, the National Collaborating Centre for Women's and Children's Health.[4] The management of eczema is also frequently reviewed.[5-8]

First-line treatment.

- Regular bathing using soap substitutes is important to *cleanse and hydrate* the skin; soaps and detergents should be avoided as these remove the natural lipid from the skin. Suitable bath oils should be used to maintain skin hydration. Emollients should be applied liberally to the whole body at least twice daily, especially after bathing, and more frequently throughout the day to hands and face. Although widely recommended, it has been noted that the use of bath emollients is not based on robust evidence and there is a need to evaluate the efficacy of such treatment.[9]
- Patients should be educated on the *avoidance of trigger factors*. These may include irritants, microbes, and psychological or allergic factors.

Acute control of pruritus and inflammation.

- Intermittent topical *corticosteroids* are the mainstay of treatment and are used for up to a week to manage acute flares of atopic eczema. Treatment for up to 6 weeks may be needed for initial control of chronic eczema. To minimise potential adverse effects the minimum strength preparation to control the disease should be used, and the age of patient, site of eczema, and extent of disease should be considered when selecting the appropriate preparation. Very potent preparations should be used in children only under specialist supervision.
- Topical *calcineurin inhibitors* (pimecrolimus or tacrolimus) may be used as alternative therapy when corticosteroids are contra-indicated, or as second-line therapy in patients who have not responded adequately to topical corticosteroids. Pimecrolimus is indicated for mild to moderate disease and tacrolimus for moderate to severe eczema. The main adverse effect is burning at the site of application. Once the condition settles the patient should revert to treatment with emollients.

Maintenance therapy.

- Topical corticosteroids may be used intermittently for acute exacerbations. Once the patient is back in remission emollients should be continued.
- For persistent disease or frequent flares, topical calcineurin inhibitors are effective and may be used at the earliest sign of recurrence. While these drugs prevent disease progression they do not have the adverse effects of corticosteroids and consequently may be used on all body areas (including sensitive areas like the face, eyelids, and neck) for extended periods. Studies so far suggest that these new drugs are safe in the short term. However, they do suppress T lymphocytes and although systemic absorption is minimal there may be a possibility of immunosuppression, skin cancers, or bacterial infection. There has been considerable debate about the possible risk of cancer associated with topical calcineurin inhibitors (see Carcinogenicity, under Tacrolimus, p. 1971.2). These concerns in particular prompted licensing authorities in Europe and the USA in 2006 to remind prescribers that these drugs should only be used intermittently as second-line treatments, and should not be used in children less than 2 years of age.[10-12]
- *Coal tar* preparations may be used occasionally for chronic atopic eczema, and *ichthammol* may be used as an ointment or paste bandages for chronic lichenified eczema.

Adjunctive therapy.

- Overt bacterial, fungal, or viral infections should be treated with an appropriate systemic drug (see Skin Infections under Antibacterials, p. 207.1, and under Antifungals, p. 568.1). Topical preparations are generally not used as they should be restricted to limited areas and patients with eczema often have widespread infections.
- A sedating *antihistamine* may be used short term for severe pruritus associated with relapse or at night-time if scratching disturbs sleep or occurs while asleep. Non-sedating antihistamines are generally ineffective in eczema but may be of benefit in atopic dermatitis and concomitant urticaria. Topical *doxepin* may provide short-term relief from pruritus, but drowsiness and contact dermatitis can occur.

Patients whose eczema fails to respond to these first-line treatments, even under specialist supervision, require further measures.

Severe refractory disease.

- *Phototherapy* with ultraviolet A or B, or in combination, may be useful, and photochemotherapy using a psoralen (generally methoxsalen) with ultraviolet A (PUVA) may be used in severe, widespread disease. However, potential long term effects such as premature ageing of the skin and skin malignancy need to be considered.
- Therapy with *more potent topical and oral corticosteroids* may be considered for short periods of time. In general, only mild corticosteroids (such as 1% hydrocortisone) should be used on the face and in flexures as absorption is increased in these areas.
- *Wet-wrap dressings* are sometimes used intermittently, particularly in children, for hydration and anti-inflammatory effects.[4,8,13,14] Different techniques have been described: wet bandages or dressings may be applied to skin already covered with an emollient or diluted corticosteroid cream, alternatively the dressing may be soaked in warm diluted cream before use; a dry outer dressing may be added. Dressings may be used only on affected parts of the body, or a whole-body suit may be used for extensive eczema, and left in place for up to 24 hours. Treatment can continue for several weeks, but should probably be limited to about 1 week when corticosteroids are used because of the risk of adverse effects from systemic absorption.[4,8,13] Wet-wrapping may not be appropriate in patients whose eczema has become infected.
- Various *other drugs* have been tried in resistant eczema. Azathioprine, ciclosporin, or methotrexate may be tried in selected patients.

Evening primrose oil and borage oil have also been tried although evidence in favour of a useful therapeutic effect is poor. Other drugs at an experimental stage include interferons, mycophenolate mofetil, and thymopentin. There has been much interest in the use of complementary and alternative therapies and herbal medicines, but serious adverse effects have occasionally occurred and although encouraging results have been reported the degree of benefit is still uncertain.[4,15,16]

1. Primary Care Dermatology Society & British Association of Dermatologists. Guidelines for the management of atopic eczema, 2006 (reviewed Jan 2010). Available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PCDS-BAD%20Eczema%20reviewed%202010.pdf (accessed 25/05/10)
2. Hanifin JM, *et al.* American Academy of Dermatology. Guidelines of care for atopic dermatitis. *J Am Acad Dermatol* 2004; 50: 391–404. Also available at: http://www.aad.org/research/_doc/ClinicalResearch_Atopic%20Dermatitis%20Part%20I.pdf (accessed 25/05/10) Correction. *ibid.* 2005; 52: 156. Also available at: http://www.aad.org/research/_doc/ClinicalResearch_Atopic%20Dermatitis%20Part%20II.pdf (accessed 25/05/10)
3. Ellis C, *et al.* International consensus conference on atopic dermatitis II (ICCAD II): clinical update and current treatment strategies. *Br J Dermatol* 2003; 148 (suppl 63): 3–10.
4. National Collaborating Centre for Women's and Children's Health/NICE. Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years (issued December 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/CG057FullGuideline.pdf (accessed 17/12/09)
5. Leung DYM, Bieber T. Atopic dermatitis. *Lancet* 2003; 361: 151–60.
6. Williams HC. Atopic dermatitis. *N Engl J Med* 2005; 352: 2314–24.
7. Brown S, Reynolds NJ. Atopic and non-atopic eczema. *BMJ* 2006; 332: 584–8.
8. Krakowski AC, *et al.* Management of atopic dermatitis in the pediatric population. *Pediatrics* 2008; 122: 812–24.
9. Anonymous. Bath emollients for atopic eczema: why use them? *Drug Ther Bull* 2007; 45: 73–5.
10. European Medicines Agency. Questions and answers on Protopic (Protopy and Elidel (issued 23 March 2006). Available at: http://www.emea.europa.eu/pdfs/general/direct/pr/8027006en.pdf (accessed 28/07/08)
11. FDA. Alert for healthcare professionals: pimecrolimus (marketed as Elidel) (issued June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm153525.htm (accessed 08/07/10)
12. FDA. Information for healthcare professionals: tacrolimus (marketed as Protopic) (issued June 2006). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm126497.htm (accessed 08/07/10)
13. Devillers ACA, Oranje AP. Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature. *Br J Dermatol* 2006; 154: 579–85.
14. Oranje AP, *et al.* Treatment of patients with atopic dermatitis using wet wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *J Eur Acad Dermatol Venereol* 2006; 20: 1277–86.
15. Armstrong NC, Ernst E. The treatment of eczema with Chinese herbs: a systematic review of randomized clinical trials. *Br J Clin Pharmacol* 1999; 48: 262–4.
16. Zuckerman GB, Bielory L. Complementary and alternative medicine: herbal therapies for atopic disorders. *Am J Med* 2002; 113 (suppl 9A): 47S–51S.

Epidermolysis bullosa

Epidermolysis bullosa consists of a group of similar congenital disorders characterised by severe blistering of the skin.[1,2] Sometimes the mucosae, especially of the mouth and oesophagus, are also affected. The blistering may be caused by various structural and metabolic defects and occurs at different levels in the skin in the different forms (simple, junctional, and dystrophic). Blistering can follow even minor trauma or can arise spontaneously. In some patients blistering and scarring can cause marked tissue loss of the affected areas and the most severe forms are fatal in early infancy because of infection of the blisters. Milder forms may be managed by avoiding trauma and keeping blisters clean and dry, but there is no truly effective treatment for the severe forms. High-dose oral corticosteroids may be needed. Phenytoin has been tried, but was unsuccessful in a controlled study. Thalidomide has also been tried, and oral tetracycline has reduced the number of lesions in a few cases.

There is also an acquired form of the disease epidermolysis bullosa acquisita, and it too is difficult to treat;[3] corticosteroids and other immunosuppressants may be tried. Individual patients have responded to high-dose intravenous immunoglobulins or extracorporeal photochemotherapy (oral methoxsalen followed by removal of blood and UV irradiation of leucocytes outside the body before reinfusion).[4,5] There are individual case reports of successful treatment with monoclonal antibodies such as basiliximab (an interleukin-2 receptor antibody)[6] and rituximab (an anti-CD20 antibody).[7]

1. Trent JT, Kirsner RS. Epidermolysis bullosa: identification and treatment. *Adv Skin Wound Care* 2003; 16: 284–90.
2. Bello YM, *et al.* Management of epidermolysis bullosa in infants and children. *Clin Dermatol* 2003; 21: 278–82.
3. Fine J-D. Management of acquired bullous skin diseases. *N Engl J Med* 1995; 333: 1475–84.
4. Miller JL, *et al.* Remission of severe epidermolysis bullosa acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 1995; 133: 467–71.
5. Gordon KB, *et al.* Treatment of refractory epidermolysis bullosa acquisita with extracorporeal photochemotherapy. *Br J Dermatol* 1997; 136: 415–20.
6. Haufs MG, Haneke E. Epidermolysis bullosa acquisita treated with basiliximab, an interleukin-2 receptor antibody. *Acta Derm Venereol (Stockh)* 2001; 81: 72.
7. Sadler E, *et al.* Treatment-resistant classical epidermolysis bullosa acquisita responding to rituximab. *Br J Dermatol* 2007; 157: 417–19.

Erythema multiforme

Erythema multiforme is an inflammatory reaction of the skin characterised by maculopapular lesions that may become annular and blister. Areas typically affected are the hands, forearms, elbows, knees, and feet. It is usually associated with a precipitating trigger such as infection (notably herpes simplex infection); it may also be associated with drug use, neoplastic disease, or collagen or inflammatory diseases. In severe forms there is also blistering of the mucous membranes (usually of the mouth). There is some overlap in the descriptions of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and attempts have been made to classify them into distinct categories.[1-4] Erythema multiforme occurs mainly after infections, whereas the Stevens-Johnson syndrome is mainly a drug-induced reaction and seems to be part of a spectrum of skin reactions, with life-threatening toxic epidermal necrolysis being the more severe form (see Drug-induced Skin Reactions, p. 1683.3).

As erythema multiforme is usually an acute reaction of relatively short duration, symptomatic treatment as for

burns (see p. 1683.1) may be all that is required. If severe reactions occur systemic corticosteroids may be considered, although there has been controversy about their value. Erythema multiforme may become a recurrent disorder in some patients and various drugs have been tried for treatment and prophylaxis.[5] Aciclovir, given in short courses or continuously, has been used particularly when herpes simplex infection appeared to be a trigger factor. Other drugs that have been tried for recurrent erythema multiforme include dapsone, hydroxychloroquine, mepacrine, azathioprine, mycophenolate, and thalidomide.

1. Assier H, *et al.* Erythema multiforme with mucous membrane involvement and Stevens-Johnson syndrome are clinically different disorders with distinct causes. *Arch Dermatol* 1995; 131: 539–43.
2. Forman R, *et al.* Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in children: a review of 10 years' experience. *Drug Safety* 2002; 25: 965–72.
3. Letko E, *et al.* Stevens-Johnson syndrome and toxic epidermal necrolysis: a review of the literature. *Ann Allergy Asthma Immunol* 2005; 94: 419–36.
4. Parrillo SJ. Stevens-Johnson syndrome and toxic epidermal necrolysis. *Curr Allergy Asthma Rep* 2007; 7: 243–7.
5. Schofield JK, *et al.* Recurrent erythema multiforme: clinical features and treatment in a large series of patients. *Br J Dermatol* 1993; 128: 542–5.

Hyperhidrosis

Hyperhidrosis (excessive sweating) can be generalised or focal, affecting the palms of the hands, soles of the feet, axillae, or less commonly the craniofacial region. No cause can usually be established although it may be secondary to an underlying endocrinological, neurological, or neoplastic disorder;[1,2] in some cases, it may be drug-induced.[3]

Drug therapy should be tried initially but is often ineffective in severe cases. Aluminium salts, such as aluminium chloride or aluminium chlorohydrate in alcoholic solvents applied topically, may be successful in milder forms of focal hyperhidrosis.[1,2,4,5] Topical antimuscarinics such as diphemanil metilsulfate, glycopyrronium bromide, or hyoscine hydrobromide may also provide some relief, particularly in craniofacial sweating.[2] Adverse effects of oral antimuscarinics generally preclude such use, although oral propantheline bromide has been used successfully to control excessive sweating in a few patients with spinal cord injuries. An intravenous infusion of phentolamine mesilate may be effective in some patients with generalised hyperhidrosis.[6] Tap water iontophoresis may be an alternative first-line option for palmar or plantar hyperhidrosis.[1,2,4] Intradermal injection of botulinum A toxin is used for focal hyperhidrosis when topical therapies are insufficient, although injections are painful and local or regional anaesthesia may be needed, especially for treatment of the hands and feet.[1,2,4,5] Formaldehyde and glutaral solutions have been used topically for hyperhidrosis affecting the feet but are not very effective and are not usually recommended.

When drug therapy fails to provide adequate relief surgery may be attempted.[1,2,4,5] Subcutaneous curettage or excision of skin bearing the eccrine glands has been used but minimally invasive techniques, notably endoscopic thoracic sympathectomy, are now available; the latter offers a simple and effective management for severe localised upper limb hyperhidrosis.

1. Hornberger J, *et al.* Recognition, diagnosis, and treatment of primary focal hyperhidrosis. *J Am Acad Dermatol* 2004; 51: 274–86.
2. Eisenach JH, *et al.* Hyperhidrosis: evolving therapies for a well-established phenomenon. *Mayo Clin Proc* 2005; 80: 657–66.
3. Cheshire WP, Fealey RD. Drug-induced hyperhidrosis and hypohidrosis: incidence, prevention and management. *Drug Safety* 2008; 31: 109–26.
4. Lowe N, *et al.* The place of botulinum toxin type A in the treatment of focal hyperhidrosis. *Br J Dermatol* 2004; 151: 1115–22.
5. Solish N, *et al.* A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg* 2007; 33: 908–23.
6. McCleane G. The use of intravenous phentolamine mesilate in the treatment of hyperhidrosis. *Br J Dermatol* 2002; 146: 533–4.

Ichthyosis

Ichthyosis is a term used for generalised noninflammatory dry scaling or keratinisation disorders (see below). There are several different forms of ichthyosis and severity and incidence varies. They are generally inherited disorders. Emollients, including urea, are used to provide relief to the dry skin by coating the skin surface with an oily film thus preventing evaporation of water. If scaling is more severe topical keratolytics such as salicylic acid or urea are used. Topical retinoids such as tazarotene may be tried. In the severest forms of ichthyosis oral retinoids may be necessary. Acitretin, etretinate, and isotretinoin have all been used. A few patients have responded to topical calcipotriol or tacrolimus, but systemic absorption may be a problem. Liarozole, an oral inhibitor of retinoic acid catabolism, has been investigated.

References.

1. Shwayder T. Ichthyosis in a nutshell. *Pediatr Rev* 1999; 20: 5–12.
2. Rubeiz N, Kibbi AG. Management of ichthyosis in infants and children. *Clin Dermatol* 2003; 21: 325–8.

Keratinisation disorders

Keratinisation is the process whereby basal epidermal cells are transformed into dead cells of the stratum corneum from where they are shed. The process takes about 14 days and shedding normally balances production so that the thickness of the stratum corneum does not alter. Keratinisation disorders (keratoses) are characterised by reduced shedding and the formation of scale at the skin surface. A scale is an aggregate of horn cells that have failed to separate horizontally and hyperkeratosis is an exaggeration of this failure in which there is also a vertical build up of the horn cells. Keratinisation disorders include Darier's disease and ichthyosis (see p. 1683.2 and above, respectively). Certain inflammatory skin disorders, such as psoriasis (see p. 1688.1), also show enhanced epidermal proliferation.

Lichen planus

Lichen planus is an inflammatory skin disorder with itchy papular lesions arising usually on the extremities. The nails and oral or buccal mucosa, and rarely the genital mucosa, may also be affected. Its cause is uncertain although sufferers have a higher incidence of auto-immune disease than normal. Some drugs can produce lichenoid reactions; examples include mepacrine, methyldopa, penicillamine, and sodium aurothiomalate.

Evidence for the efficacy of the various treatments that have been tried is mostly scanty.[1-3] In most patients lichen planus remits spontaneously and, if mild and localised, little or no treatment is needed. Potent topical corticosteroids are often used for localised cutaneous disease when treatment is needed, and occlusive dressings may be used to enhance efficacy.[1,4] However, less potent corticosteroids should generally be used on the face, axillae, groin, or genitals. Intralesional corticosteroids, such as triamcinolone acetonide, can be used for hyperkeratotic or resistant localised plaques. Symptomatic mucosal disease is also treated with topical corticosteroids;[1,3-5] various dosage forms have been used including ointments, adhesive bases, pastes, lozenges, and mouthwashes. Other drugs that have been used topically, with variable results, include ciclosporin and the retinoids isotretinoin and tretinoin. Intralesional corticosteroids have also been used for resistant or erosive mucosal lesions.[1,5]

Systemic corticosteroids may be used in generalised cutaneous lichen planus and acute exacerbations of mucosal disease.[1,3-5] If the condition becomes resistant to corticosteroid therapy, an oral retinoid such as acitretin, etretinate, or isotretinoin, may be tried. Other oral treatments for which there are reports of benefit in small numbers of patients include ciclosporin, griseofulvin, chloroquine and hydroxychloroquine, and photochemotherapy using a psoralen with UVA (PUVA).[1,3] Topical tacrolimus and pimecrolimus have also been tried.[3]

1. Cribier B, *et al.* Treatment of lichen planus: an evidence-based medicine analysis of efficacy. *Arch Dermatol* 1998; 134: 1521–30.
2. Zakrzewska JM, *et al.* A systematic review of placebo-controlled randomized clinical trials of treatments used in oral lichen planus. *Br J Dermatol* 2005; 153: 336–41.
3. Farhi D, Dupin N. Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. *Clin Dermatol* 2010; 28: 100–108.
4. Katta R. Lichen planus. *Am Fam Physician* 2000; 61: 3319–24, 3327–8. Correction. *ibid.*; 62: 1786.
5. Agarwal R, Saraswat A. Oral lichen planus: an update. *Drugs Today* 2002; 38: 533–47.

Lichen sclerosus

Lichen sclerosus is a chronic inflammatory skin condition that most commonly occurs in women, but is also seen in men and children.[1-6] It affects the anogenital area, causing itching, soreness, and urinary and sexual problems. Extragenital lesions may occur, but do not usually itch, and some patients may show no symptoms at all.[1,3,6] Lichen sclerosus runs a relapsing and remitting course and complications include secondary infection, most commonly with *Candida*, physical scarring, and vulvodynia. The most common complication seen in male patients is phimosis. Although the exact cause of the disease is unknown, there appears to be a strong association with auto-immune disorders and genetic factors have also been implicated. There is also an association between lichen sclerosus and squamous cell and verrucous carcinoma.[1,3,4,6]

Management of lichen sclerosus includes the control of symptoms, prevention and treatment of complications, and the early detection of malignancies.[1,3,4,6] Emollients and soap substitutes are recommended. Topical potent corticosteroids such as clobetasol propionate or betamethasone dipropionate 0.05% have been shown to be safe and effective for both genital and extragenital disease. Intralesional triamcinolone was found to be effective in a small study. The benefit and safety of other topical treatments, such as pimecrolimus, tacrolimus, retinoids, testosterone, and progesterone are not clear. However, recent reviews[7,8] concluded that pimecrolimus and tacrolimus may be useful second-line drugs for patients who are resistant to topical corticosteroids. Systemic retinoids may be useful in complicated disease that is not responding to topical corticosteroids. There have been reports of benefit for treatment with stanozolol, photochemotherapy using a psoralen with UVA (PUVA), photodynamic therapy using topical 5-aminolevulinic acid, and laser therapy. Surgical intervention is only indicated for complications of scarring or the development of malignancy.[1,3,4,6]

1. Tasker GL, Wojnarowska F. Lichen sclerosus. *Clin Exp Dermatol* 2003; 28: 128–33.
2. McLelland J. Lichen sclerosus in children. *J Obstet Gynaecol* 2004; 24: 733–5.
3. Yesudian PD, *et al.* Lichen sclerosus. *Int J STD AIDS* 2005; 16: 465–73.
4. Dalziel K, Shaw S. Lichen sclerosus. *BMJ* 2010; 340: 759–61.
5. Smith SD, Fischer G. Paediatric vulval lichen sclerosus. *Australas J Dermatol* 2009; 50: 243–8.
6. Neill SM, *et al.* British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. *Br J Dermatol* 2010; 163: 672–82. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Lichen%20Sclerosus%20Guidelines%202010.pdf (accessed 31/01/11)
7. Goldstein AT, *et al.* Topical calcineurin inhibitors for the treatment of vulvar dermatoses. *Eur J Obstet Gynecol Reprod Biol* 2009; 146: 22–9.
8. Yesudian PD. The role of calcineurin inhibitors in the management of lichen sclerosus. *Am J Clin Dermatol* 2009; 10: 313–18.

Light-induced skin reactions

Light, although essential for many biological functions, may cause a variety of disorders, particularly due to the ultraviolet portion of the solar spectrum.

Ultraviolet (UV) light has different properties according to its wavelength.

- **UVA** (wavelengths 320 to 400 nm) produces immediate direct tanning of the skin with little erythema although it does contribute to the long-term harmful effects of photoageing and cancers. UVA has also been subdivided into UVA-I (340 to 400 nm) and UVA-II (320 to 340 nm); the effects of UVA-II are more like those of UVB.
- **UVB** (wavelengths 290 to 320 nm) is about 1000 times stronger than UVA in producing erythema and is that part of the sun's spectrum that is responsible for producing sunburn and it too contributes to long-term effects. UVB also produces tanning by indirect pigmentation.
- **UVC** (wavelengths 200 to 290 nm) produces erythema without tanning. The earth's surface is usually screened by the ozone layer from UVC radiation although UVC may be emitted by artificial sources such as bactericidal lamps and industrial welding arcs.

In normal healthy individuals **exposure to sunlight** (including reflected light from snow, white sand, or water) causes an increase in pigmentation (tanning). This is an adaptive mechanism to protect the skin from UV radiation. Immediate tanning results from the oxidation of melanin precursors in the uppermost layers of the skin. There may also be a delayed and indirect pigmentation due to the formation of new melanin. The ability of an individual to form a tan is genetically predetermined. Melanin provides some protection against further exposure, but the main protection is provided by thickening of the corneous layer. However, excessive exposure to strong sunlight causes erythema and sunburn, which is an inflammatory response to the damage caused by UV radiation.

Excessive and prolonged exposure to intense sunlight may lead to degenerative changes in the skin (premature ageing of the skin or photoageing, p. 1686.2), actinic (solar) keratoses (which are risk factors or precursors of skin cancers), immunosuppression, and some skin cancers such as basal cell or squamous cell carcinomas and malignant melanomas (see Malignant Neoplasms of the Skin, p. 714.1). Some patient groups are also at higher risk of adverse effects from sunlight exposure. Even brief exposure to sunlight can trigger a reaction in those with photosensitivity disorders (p. 1686.2), patients with hypopigmentation disorders such as vitiligo and albinism (see Pigmentation Disorders, p. 1687.2) are more susceptible to sunburn, and transplant patients receiving systemic immunosuppressants are at increased risk of skin cancers (see under Organ and Tissue Transplantation, p. 1932.2). Many drugs can cause a phototoxic or photoallergic reaction (see Drug-induced Photosensitivity, p. 1686.1).

Protection against sunlight is therefore beneficial, both in healthy people to prevent skin damage, and in patients at increased risk of adverse effects from sunlight exposure. Medical and scientific personnel exposed to ultraviolet lamps may need protection against the whole of the UV spectrum. This may be achieved by appropriate dress and through the use of **sunscreens** applied to the skin. Sunscreens may be of chemical or physical types (see p. 1681.3) and many products combine sunscreens of different types to maximise protection. A broad-spectrum sunscreen should be effective against both UVA and UVB, but UVA coverage can be variable. It may be difficult to formulate physical sunscreens in cosmetically acceptable ways.

The efficacy of a particular sunscreen preparation is often expressed as its **sun protection factor (SPF).** This is a ratio of the time required for irradiation to produce minimal perceptible erythema (minimal erythemal dose; MED) with the skin protected with the sunscreen compared with the MED without protection, for a standard 2 mg/cm² dose of sunscreen. Thus the SPF is mainly an indication of efficacy against UVB light. Various systems have been suggested for classifying the relative efficacies of sunscreens against UVA light but none appears, as yet, to be universally accepted. The efficacy of a sunscreen is also highly dependent upon its correct application and studies have found that, in general, sunscreen preparations are applied haphazardly and in insufficient quantities to provide optimal protection.

Governmental authorities and dermatologists in many countries issue guidance to the public on sun protection, including sunscreen use. General measures include avoiding sunlight exposure when UV radiation is strongest (usually between 10 a.m. and 3 p.m.), seeking shade when outdoors in strong sunlight, using wrap-around sunglasses that conform to appropriate standards, and wearing a broad-brimmed hat and clothing that protect against sunlight. Sunscreens should be applied liberally and evenly to all exposed areas of skin at least 15 to 30 minutes before sunlight exposure, and re-applied at least every 2 hours and after swimming or perspiring. Broad-spectrum products are recommended; dermatologists in some countries such as the UK and USA advocate the use of preparations with at least SPF 15 (SPF 15+), while in Australia SPF 30+ is recommended.

Many treatments have been tried in the management of acute *sunburn*, but studies have been small and results often conflicting. There is a lack of strong evidence to show that any specific treatment reduces epidermal damage or the time to healing once the signs and symptoms of sunburn have developed. Emollients, cool compresses, paracetamol, and NSAIDs, are often used for symptomatic relief of erythema, pain, and pruritus; oral antihistamines, topical hydrocortisone, and topical anaesthetics might also be considered.

Reviews.

1. Gasparro FP. Sunscreens, skin photobiology, and skin cancer: the need for UVA protection and evaluation of efficacy. *Environ Health Perspect* 2000; 108 (suppl): 71–8.
2. Moloney FJ, *et al.* Sunscreens: safety, efficacy and appropriate use. *Am J Clin Dermatol* 2002; 3: 185–91.
3. Anonymous. Prevention and treatment of sunburn. *Med Lett Drugs Ther* 2004; 46: 45–6.
4. Han A, Maibach HI. Management of acute sunburn. *Am J Clin Dermatol* 2004; 5: 39–47.
5. Maier T, Korting HC. Sunscreens–which and what for? *Skin Pharmacol Physiol* 2005; 18: 253–62.
6. Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. *Dermatol Clin* 2006; 24: 35–51.
7. Osterwalder U, Herzog B. Sun protection factors: world wide confusion. *Br J Dermatol* 2009; 161 (suppl 3): 13–24.

Drug-induced photosensitivity. Photosensitivity can be produced by drugs either given systemically or applied topically, and the reaction can be phototoxic or photoallergic in nature.[1] In *phototoxicity*, a direct toxic effect on tissues occurs when the drug is energised by absorbing radiation. The reaction has a rapid onset (usually within 24 hours) and occurs on exposed skin areas. Resembling an exaggerated sunburn, the reaction can include erythema, oedema, hyperpigmentation causing a darker red than sunburn, pruritus, and urticaria. The response is dependent on the dose of the photosensitiser and the intensity of sunlight exposure. In *photoallergy*, the hypersensitivity reaction has an immunological basis requiring previous exposure to the photosensitising drug. The onset may be delayed until several days after exposure to sunlight and present as a papulovesicular eruption, pruritus, and eczematous dermatitis. Photoallergic reactions are less common than phototoxicity.

Systemic drug groups that have been reported to cause photosensitivity include:

- antibacterials (fluoroquinolones, sulfonamides, and tetracyclines)
- antidepressants (tricyclic antidepressants and St John's wort)
- antiepileptics (carbamazepine, lamotrigine, phenobarbital, and phenytoin)
- antihistamines (including cyproheptadine, diphenhydramine, and loratadine)
- antimalarials (chloroquine, quinine, pyrimethamine, and mefloquine)
- antineoplastics (including fluorouracil, methotrexate, and vinblastine)
- cardiovascular drugs (including ACE inhibitors, amiodarone, quinidine, thiazide diuretics, and simvastatin)
- corticosteroids
- NSAIDs
- phenothiazine antipsychotics
- sex hormones (oestrogens and progestogens)
- sulfonylurea antidiabetic drugs
- retinoids (isotretinoin)

Photocontact dermatitis occurs from the interaction between sunlight and topically applied substances, and can be either a phototoxic or photoallergic reaction. Implicated drugs have included antiseptics, antifungals, coal tar, corticosteroids, local anaesthetics, and retinoids.[1] Photosensitivity reactions have also occurred to the topical sunscreens intended to prevent them.[1,2] Photoallergic reactions have been reported for chemical sunscreens, particularly aminobenzoic acid and benzophenones (dioxybenzone, mexenone, oxybenzone, and sulisobenzone). Reactions to cinnamates seem to be less frequent.

Photosensitivity reactions are managed symptomatically as for sunburn (see Light-induced Skin Reactions, p. 1685.3); antihistamines and corticosteroids may be needed to treat photoallergic reactions. If the offending drug cannot be withdrawn or substituted, sun exposure should be minimised with appropriate clothing and sunscreens.[1]

1. Moore DE. Drug-induced cutaneous photosensitivity: incidence, mechanism, prevention and management. *Drug Safety* 2002; 25: 345–72.
2. Scheuer E, Warshaw E. Sunscreen allergy: a review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis* 2006; 17: 3–11. Correction. *ibid.*; 162.

Photoageing. Exposure to sunlight induces changes in the skin in addition to the normal ageing process. This photoageing, or photodamage, can manifest as wrinkles, skin roughness and dryness, irregular pigmentation, telangiectasia, sallowness, and lentigines (sun or liver spots). Photoageing is also associated with increased risks of actinic keratoses and skin cancers (see Malignant Neoplasms of the Skin, p. 714.1).

Cosmetic treatments and procedures for the effects of photoageing have been extensively and widely promoted, but few have undergone rigorous scientific evaluation and there is a lack of data in general.[1] Measures to limit sunlight exposure, including the use of sunscreens, reduce the progression of photoageing.[2,3] Topical retinoids, such as isotretinoin, tazarotene, and tretinoin, can improve fine wrinkles, irregular pigmentation, roughness, and lentigines. However, the effect is dose-related and these drugs can cause irritation and photosensitivity.[1–4] Hydroxyacid keratolytics such as glycolic acid are also widely promoted for the reduction of photoageing effects. Low concentrations are used in nonprescription cosmetic preparations, and higher concentrations may be used as chemical peels. Overall, however, their effects are limited.[1,2] Local injection of botulinum A toxin to cause muscle paralysis is used for the cosmetic reduction of lines and wrinkles.[2,3] Injectable skin fillers such as bovine collagen and hyaluronic acid are also available to reduce lines and deep wrinkles.[2] Other procedures in use include dermabrasion to reduce wrinkles, and cryosurgery or electrosurgery for discrete pigmented lesions; lasers or other light therapies are also used for wrinkles, pigmented lesions, and benign vascular proliferations such as telangiectasia and angiomas.[2] Topical photodynamic therapy may have a role in photorejuvenation.[5] Oral and topical antoxidants have also been promoted for the treatment and prevention of photoageing, but there is a lack of data to support such claims.[2,3]

1. Samuel M, *et al.* Interventions for photodamaged skin. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2005 (accessed 25/09/07).
2. Stern RS. Treatment of photoaging. *N Engl J Med* 2004; 350: 1526–34.
3. McCullough JL, Kelly KM. Prevention and treatment of skin aging. *Ann N Y Acad Sci* 2006; 1067: 323–31.
4. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; 65: 1061–72.
5. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; 159: 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 01/06/10)

Photosensitivity disorders. In some persons even brief exposure to sunlight can result in light-induced disorders of the skin.

Polymorphic light eruption is a common hypersensitivity reaction characterised by pruritic erythematous papulovesicular lesions that develop several hours after exposure to sunlight. The condition usually begins in adulthood and affects more women than men. For many patients the susceptibility to eruption starts in early spring and resolves by late summer as the skin becomes more tolerant to sunlight, but patients with severe forms may also be symptomatic in the winter. Mild forms can settle without scarring within days, by sun avoidance and use of a broad-spectrum sunscreen. Potent topical corticosteroids or a short course of oral prednisolone may be useful to control the acute rash. A gradual increase in exposure to sunlight may be sufficient for desensitisation in mild cases, but patients with more severe disease may need to undergo artificial hardening of the skin by UVB phototherapy or photochemotherapy using a psoralen with UVA (PUVA). However, this effect is temporary and usually needs to be repeated each spring.[1–4] Azathioprine may be considered in patients who are very sensitive to sunlight, for whom sunscreens are ineffective, and who cannot tolerate phototherapy.[2]

Chronic actinic dermatitis is manifested by a persistent, often lichenified, eczematous eruption that usually only affects the exposed areas although in a small number of patients larger areas can be affected. It mainly affects older men, and many patients may be unaware of the role that sunlight plays in the condition. These patients may also show clinically relevant allergy to many naturally occurring substances, as well as drugs and sunscreens.[3,5,6] Management is based on sunlight and allergen avoidance and the use of sunscreens, emollients, and topical or oral corticosteroids. Phototherapy or photochemotherapy may also be useful. Systemic immunosuppressants including azathioprine, ciclosporin, and mycophenolate mofetil have been used in resistant disease.[1,4–6] Interferon alfa and topical tacrolimus have also been used successfully in a few cases.[1]

Actinic prurigo is similar to polymorphic light eruption but less common, and is characterised by persistent pruritic papules on areas exposed to sunlight, often with extension to covered areas. Other features include scarring, cheilitis and eye involvement. It is managed similarly with sunscreens, topical or oral corticosteroids, and phototherapy or photochemotherapy. Thalidomide has been used, but relapse frequently occurs when treatment is stopped.[1,4]

Solar urticaria is an uncommon condition that can often be managed with sunscreens alone, but non-sedating antihistamines such as loratadine may also be helpful. Phototherapy and photochemotherapy have also been used.[1,4]

Xeroderma pigmentosum is a rare autosomal recessive condition in which a defective DNA-repair system fails to repair UV-induced DNA damage.[7] The skin is hypersensitive to sunlight, resulting in serious sunburn after minimal exposure. From a very early age patients start to develop lentigines (sun or liver spots), spotty hypopigmentation, telangiectasias, calloused thickening, atrophy, scabbing, and scarring. Numerous actinic keratoses, precancerous lesions, and malignant neoplasms of the skin (p. 714.1) develop in childhood and many patients die before reaching adulthood. Other effects of the disease include motor impairment, mental retardation, ocular damage, leukaemia, and dental caries. Management involves strict avoidance of sunlight and use of broad-spectrum sunscreens. There is some evidence that systemic retinoids, such as acitretin and isotretinoin, may be useful in preventing the development of skin cancers, although adverse effects from long-term use may be of concern. Topical fluorouracil may be used on actinic keratoses and malignant skin cancers. A topical preparation containing recombinant T4 endonuclease V, a DNA-repair enzyme, is under investigation to reduce the incidence of actinic keratoses and skin cancers.

Other conditions that can be exacerbated by sunlight include the cutaneous porphyrias (p. 1556.1), lupus erythematosus (p. 1613.3), and sometimes herpes labialis (p. 955.2).

1. Ferguson J. Diagnosis and treatment of the common idiopathic photodermatoses. *Australas J Dermatol* 2003; 44: 90–6.
2. Ling TC, *et al.* Treatment of polymorphic light eruption. *Photodermatol Photoimmunol Photomed* 2003; 19: 217–27.
3. Morison WL. Photosensitivity. *N Engl J Med* 2004; 350: 1111–17.
4. Bylaite M, *et al.* Photodermatoses: classification, evaluation and management. *Br J Dermatol* 2009; 161 (suppl 3): 61–8.
5. Hawk JLM. Chronic actinic dermatitis. *Photodermatol Photoimmunol Photomed* 2004; 20: 312–14.
6. Dawe RS. Chronic actinic dermatitis in the elderly: recognition and treatment. *Drugs Aging* 2005; 22: 201–7.
7. Norgauer J, *et al.* Xeroderma pigmentosum. *Eur J Dermatol* 2003; 13: 4–9.

Molluscum contagiosum

Molluscum contagiosum is a poxvirus infection that produces small (1 to 2 mm) pearly-white or flesh-coloured papules that are smooth and dome-shaped with central umbilication. The lesions are usually found on the skin but can appear in mucosal areas, mainly the genital mucosa and conjunctiva. The infection is highly contagious, being spread through physical contact and other modes such as shared bathtubs and towels, and is most prevalent in schoolchildren. Individual lesions tend to persist for only a few weeks, and in most children the natural course of infection is spontaneous clearance within 2 to 4 years of onset. However, immunocompromised patients are more likely to develop extensive disease.[1]

For most patients, no treatment is necessary and the condition will eventually clear, although symptomatic therapy including topical corticosteroids and antihistamines may be needed if there is pruritus, eczematous symptoms, or inflammation. Treatment of the lesions may be indicated in immunocompromised patients and in those with extensive lesions, who are at increased risk of scarring. Local destruction of individual lesions may be achieved using topical cantharidin, cryosurgery, or curettage.[1] In adults with genital molluscum contagiosum, piercing of the lesions with or without application of tincture of iodine or phenol may be considered; topical podophyllotoxin is another alternative for genital skin lesions in men.[2] Cimetidine and topical imiquimod have been tried as immunomodulators.[1] HAART used in patients with HIV

infection can promote clearance of molluscum contagiosum, and topical cidofovir has also been tried in patients with HIV infection.[1] However, clear evidence to support any form of treatment is lacking.[3]

1. Brown J, *et al.* Childhood molluscum contagiosum. *Int J Dermatol* 2006; 45: 93–9.
2. Clinical Effectiveness Group (British Association of Sexual Health and HIV). United Kingdom national guideline on the management of molluscum contagiosum (2007). Available at: http://www.bashh.org/documents/26/26.pdf (accessed 01/06/10)
3. van der Wouden JC, *et al.* Interventions for cutaneous molluscum contagiosum. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2009 (accessed 01/06/10).

Pemphigus and pemphigoid

Pemphigus and pemphigoid are rare, disabling, and severe or potentially fatal blistering skin diseases. They are distinct disorders although both have an auto-immune basis. Some drugs might also trigger pemphigus or pemphigoid; implicated drugs have included penicillamine and ACE inhibitors.

- There are several types of pemphigus. In pemphigus vulgaris, the most common type, the blistering is intra-epidermal and can occur anywhere on the skin surface or present as ulceration of the mucous membranes. It is a chronic, progressive disorder requiring prolonged treatment.
- Pemphigoid is also known as bullous pemphigoid and occurs mainly in elderly persons. The blistering is subepidermal and affects the skin; mucous membranes can be affected in up to a half of all patients but it may be mild and not noticed by the patient. Pemphigoid is usually a self-limiting disorder and treatment can often be stopped after a couple of years.
- Mucous membrane pemphigoid (cicatricial pemphigoid) is a rare form that affects mainly the oral mucosa and conjunctiva, and may affect other mucosae, causing scarring.

The treatment of the blistering in both pemphigus and pemphigoid follows a similar pattern. Wet dressings and general treatment as for burns (see p. 1683.1) are commonly used. Corticosteroids are used initially to induce remission. Maintenance treatment often includes adjunctive therapies aimed at keeping control of the disease while tapering the corticosteroid dose, with the ultimate aim of complete treatment withdrawal.

High doses of systemic corticosteroids may be required to control the blistering, which may take weeks.[1-3] The optimum dose has not been established and suggestions have varied enormously (for more detail see Pemphigus and Pemphigoid, under Corticosteroids, p. 1610.1); very high doses of oral prednisolone have been used in the past.[2] Pulsed intravenous corticosteroids such as methylprednisolone may be considered for severe or refractory disease, particularly if there has been no response to high oral doses.[2,3] A very potent topical corticosteroid such as clobetasol propionate can be sufficient to control localised or mild to moderate disease in some patients, particularly in bullous pemphigoid.[1,3-5] Blistering and ulceration of the oral mucous membranes may be treated with topical corticosteroid preparations.[2,3,6] Intralesional injections have also been used for isolated lesions of the skin[3] and oral mucosa.[3,6] Topical corticosteroids may need to be added to initial systemic therapy to control acute ocular inflammation.[7]

Various therapies have been used as adjuncts or occasionally as alternatives to treatment with corticosteroids. However, given the rarity of the diseases, few controlled studies have been performed. Immunosuppressive therapy, usually with azathioprine, may be added to improve disease control and permit a reduction in corticosteroid dosage.[1,2,4,6] Cyclophosphamide and methotrexate have been used similarly although there is less information published about their use.[1,2,4,8] Oral or intravenous cyclophosphamide with a corticosteroid may be useful in severe or rapidly progressing mucous membrane pemphigoid.[6] Chlorambucil might be considered if other immunosuppressants cannot be used, but there is very limited evidence to support this.[1,2] Mycophenolate mofetil and ciclosporin have also been used in small numbers of patients with some reports of success.[1,2,4,6] Some patients with bullous pemphigoid respond to dapsone,[1,4] and it may be adequate for first-line treatment in mild to moderate inflammation in mucous membrane pemphigoid.[6,7] A tetracycline, alone or with nicotinamide, may be useful in controlling the lesions of various types of pemphigus and pemphigoid. They may be tried in patients with mild to moderate disease.[1,2,4] Intramuscular gold therapy has also been used for pemphigus vulgaris, and might be considered when other adjunctive drugs cannot be used.[2] High-dose intravenous immunoglobulin has been given to permit reduction of corticosteroid therapy in pemphigus and pemphigoid, and in some patients has produced prolonged remission.[9] It is usually reserved for severe disease that has not responded to other therapies.[2,4] Rituximab has induced remission in previously unresponsive pemphigus.[3,10-12] Plasmapheresis (plasma exchange) may be tried in severe, unresponsive disease,[1,2] but there is little evidence of benefit and its use can be limited by cost and adverse effects.[4]

1. Wojnarowska F, *et al.* British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002; 147: 214–21. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Bullous%20Pemphigoid.pdf (accessed 20/07/10)
2. Harman KE, *et al.* British Association of Dermatologists. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003; 149: 926–37. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Pemphigus%20Vulgaris.pdf (accessed 20/07/10)
3. Bryssryn J-C, Rudolph JL. Pemphigus. *Lancet* 2005; 366: 61–73.
4. Walsh SRA, *et al.* Bullous pemphigoid: from bench to bedside. *Drugs* 2005; 65: 905–26.
5. Khumalo N, *et al.* Interventions for bullous pemphigoid. Available in the Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2005 (accessed 25/09/07).
6. Sacher C, Hunzelmann N. Cicatricial pemphigoid (mucous membrane pemphigoid): current and emerging therapeutic approaches. *Am J Clin Dermatol* 2005; 6: 93–103.
7. Laforest C, *et al.* Autoimmune bullous diseases: ocular manifestations and management. *Drugs* 2005; 65: 1767–79.
8. Gürcan HM, Ahmed AR. Analysis of current data on the use of methotrexate in the treatment of pemphigus and pemphigoid. *Br J Dermatol* 2009; 161: 723–31.
9. Ahmed AR. Use of intravenous immunoglobulin therapy in autoimmune blistering diseases. *Int Immunopharmacol* 2006; 6: 557–78.
10. Cianchini G, *et al.* Severe persistent pemphigoid gestationis: long-term remission with rituximab. *Br J Dermatol* 2007; 157: 388–9.
11. Fernando SL, O'Connor KS. Treatment of severe pemphigus foliaceus with rituximab. *Med J Aust* 2008; 189: 289–90.
12. Jensen AØ, *et al.* Treatment of treatment-resistant autoimmune blistering skin disorders with rituximab. *Br J Dermatol* 2009; 160: 1359–61.

Pigmentation disorders

The pigment melanin is produced in melanocytes in the basal layer of the epidermis. It is a complex polymer synthesised from the amino acid, dihydroxyphenylalanine. Melanin production is under pituitary control but is also influenced by other endocrine secretions.

Decreased pigmentation (hypopigmentation) and excessive pigmentation (hyperpigmentation) can occur and may be either generalised or localised.

Albinism is a rare inherited disorder that can cause generalised **hypopigmentation**. Affected individuals are extremely sensitive to solar irradiation and must use sunscreens regularly.

A common form of localised hypopigmentation is **vitiligo**. Sharply defined areas of depigmentation are seen and may remain localised or spread so that total depigmentation eventually occurs. Depigmented areas are more susceptible to sunburn and all exposed areas, both normal and depigmented, should be protected from sunlight with clothing or sunscreens. Cosmetic camouflage of the depigmented area is commonly used, and may be sufficient for patients when only small affected areas are visible.[1] Dihydroxyacetone produces a brown staining of the skin that may be cosmetically acceptable. There is no totally effective repigmentation treatment, although some therapies may offer a degree of benefit. Topical corticosteroids are sometimes effective at inducing repigmentation,[2,3] and it is recommended that these be considered for a trial period of no more than 2 months.[1] Topical pimecrolimus has been suggested as an alternative to topical corticosteroids.[1] Narrowband UVB phototherapy or photochemotherapy with psoralens (PUVA) is recommended only in patients who cannot be managed with more conservative treatments, who have widespread vitiligo, or who have localised vitiligo with significant impact on their quality of life.[1] It is suggested that this treatment be reserved for patients with darker skin types.[1] Some consider UVB phototherapy to be superior to the use of UVA,[2,3] and the initial treatment of choice in moderate to severe disease,[4] or in non-segmental vitiligo.[1] Experimental drug therapy for re-inducing pigment has included UVA light therapy with either khellin or phenylalanine; oral levamisole, alone or with topical corticosteroids, has also been reported to be of benefit. There are a few small studies and case reports of benefit with the use of topical tacrolimus[4,5] and combinations of topical calcipotriol with either UV light therapy or a corticosteroid.[4] Various grafting techniques are recommended in patients for whom surgical treatment is appropriate.[1] Transplantation of autologous cultured melanocytes, ultrathin epidermal sheets, or basal cell layer suspension may be beneficial in some forms of vitiligo. The optimal transplant procedure is autologous epidermal suspension applied to laser-abraded lesions followed by narrow band UVB or PUVA therapy.[1] Transplantation is not suitable for progressive, widespread vitiligo vulgaris.[3,6] If the vitiligo affects a large proportion of the body (more than 50%), and if PUVA is ineffective at inducing repigmentation, an option is to consider inducing depigmentation in the remaining normal skin in order to match the lighter vitiligous areas.[1] Permanent depigmentation may be induced by monobenzone,[1] but patients must subsequently use topical sunscreens in order to avoid damage caused by solar exposure.

Hyperpigmentation can be caused by increased amounts of melanin, or by other substances such as iron in the skin. Generalised hyperpigmentation may be seen in Addison's disease, acanthosis nigricans, and primary haemochromatosis; other causes may include cirrhosis, chronic renal failure, and glycogen storage disease. Darkening of the skin can also occur in patients taking certain drugs due to a deposition of the drug-melanin complex in the skin. Notable examples include amiodarone, minocycline, and phenothiazines. Localised hyperpigmentation is seen in chloasma (melasma) in which there is facial involvement and is encountered most commonly in pregnancy; it may also be associated with hormonal contraceptive use. Several compounds have been used basically as bleaching agents in hyperpigmentary disorders, and of these hydroquinone has been used most often;[7,8] monobenzone is not recommended. A beneficial response to topical tretinoin and azelaic acid in patients with chloasma has been described. Combination preparations containing hydroquinone, tretinoin, and a corticosteroid are available in some countries. Laser therapy, or the use of chemical peels, has also been tried.[7,8]

1. Gawkrodger DJ, *et al.* Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Clinical Standards Department, Royal College of Physicians of London. Cochrane Skin Group. Vitiligo Society. Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 2008; 159: 1051–76. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Vitiligo%202008.pdf (accessed 25/05/10)
2. Njoo MD, *et al.* Nonsurgical repigmentation therapies in vitiligo: meta-analysis of the literature. *Arch Dermatol* 1998; 134: 1532–40.
3. Hartmann A, *et al.* Hypopigmentary skin disorders: current treatment options and future directions. *Drugs* 2004; 64: 89–107.
4. Grimes PE. New insights and new therapies in vitiligo. *JAMA* 2005; 293: 730–5.
5. Kostovic K, Pasic A. New treatment modalities for vitiligo: focus on topical immunomodulators. *Drugs* 2005; 65: 447–59.
6. Olsson MJ, Juhlin L. Long-term follow-up of leucoderma patients treated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. *Br J Dermatol* 2002; 147: 893–904.
7. Grimes PE. Melasma: etiologic and therapeutic considerations. *Arch Dermatol* 1995; 131: 1453–7.
8. Rendon M, *et al.* Treatment of melasma. *J Am Acad Dermatol* 2006; 54 (suppl): S272–S281.

Pruritus

Pruritus (itching) is a common and distressing symptom of many skin disorders but may also have a systemic cause such as obstructive jaundice, chronic renal disease, endocrine disease, certain malignancies, or a drug hypersensitivity reaction. The exact pathophysiology of itching is unclear, and different inflammatory mediators may be associated with itching in different disorders; the CNS is also thought to play a role in the perception of itch.

Pruritus should be considered as symptomatic of the underlying disorder and treatment should focus on the removal of the offending trigger. However, symptomatic treatment of pruritus may also be necessary.

Emollients may be useful where dry skin is a contributory factor, and may be applied for topical management of pruritus. Calamine and crotamiton are often used topically, despite some uncertainty about their value, as are preparations containing phenol or agents such as menthol that cause capillary dilatation with a subsequent sensation of cold and analgesia. Topical capsaicin has also been used and topical corticosteroids may be used to relieve pruritus when there is associated inflammation. Local anaesthetics or antihistamines are only marginally effective for topical use and can very occasionally cause sensitisation. However, lauromacrogol 400 has proved of benefit. Doxepin, a tricyclic antidepressant with very potent antihistaminic activity, has been used topically for the relief of pruritus associated with dermatitis, but adverse effects from systemic absorption can limit its use.

Sedating antihistamines given orally are commonly used to relieve more generalised pruritus and are used to control the severe itching associated with dermatoses such as atopic eczema (see p. 1684.1). Mirtazapine, a noradrenergic and serotonergic antidepressant with a potent antihistamine effect, has been tried in various types of pruritus with reports of success. Bile-acid binding resins, such as colestyramine, are used to relieve pruritus associated with the deposition in dermal tissue of excess bile acids in patients with partial biliary obstruction, primary biliary cirrhosis, or intrahepatic cholestasis of pregnancy. There are reports of cholestatic pruritus also responding to ondansetron although results from controlled studies have been mixed. Rifampicin has also been used. Pruritus caused by obstetric cholestasis has been treated with ursodeoxycholic acid, which also corrects the associated biochemical abnormalities. Central opioid receptors modulate itch and opioid antagonists such as nalmefene and naltrexone have been reported to relieve pruritus. Many other drugs, including cimetidine, gabapentin, and propofol, have been of benefit in some patients. Paroxetine has been useful in

some patients with cancer-related pruritus, but the effect tended to wear off after several weeks. PUVA (see under Methoxsalen, p. 1712.1) may be helpful in some pruritic skin conditions including aquagenic pruritus.

References.
1. Jenkins JK, Boothby LA. Treatment of itching associated with intrahepatic cholestasis of pregnancy. *Ann Pharmacother* 2002; 36: 1462–5.
2. Yosipovitch G, *et al.* Itch. *Lancet* 2003; 361: 690–4.
3. Twycross R, *et al.* Itch: scratching more than the surface. *Q J Med* 2003; 96: 7–26.
4. Summey BT, Yosipovitch G. Pharmacologic advances in the systemic treatment of itch. *Dermatol Ther* 2005; 18: 328–32.
5. Hercogová J. Topical anti-itch therapy. *Dermatol Ther* 2005; 18: 341–3.
6. Bergasa NV. Medical palliation of the jaundiced patient with pruritus. *Gastroenterol Clin North Am* 2006; 35: 113–23.
7. Cles JJ, Glamalis JN. Treatment of cholestatic pruritus in children. *Am J Health-Syst Pharm* 2007; 64: 1157–62.
8. Kremer AE, *et al.* Pathogenesis and treatment of pruritus in cholestasis. *Drugs* 2008; 68: 2163–82.
9. Manenti L, *et al.* Uraemic pruritus: clinical characteristics, pathophysiology and treatment. *Drugs* 2009; 69: 251–63.
10. Vila T, *et al.* Role of gabapentin in the treatment of uremic pruritus. *Ann Pharmacother* 2008; 42: 1080–4.

Psoriasis

Psoriasis is a chronic inflammatory skin disorder characterised by enhanced epidermal proliferation leading to erythema, scaling, and thickening of the skin. It appears to be a T-cell mediated auto-immune disease. There are several types of psoriasis including guttate, flexural, pustular, and erythrodermic, but chronic plaque psoriasis (psoriasis vulgaris) is the most common form. In chronic plaque psoriasis the areas most commonly affected are the extensor sides of the knees, elbows, and hands, and the scalp and sacrum. There is no cure and treatment is designed to induce a remission or suppress disease to a tolerable level.

The treatment of psoriasis has been the subject of many reviews.[1-9]

Topical drugs are the treatment of first choice for chronic plaque psoriasis. Mild conditions may be managed with the use of emollients alone but dithranol, coal tar, calcipotriol, or tazarotene are the usual active treatments for mild to moderate forms. Patients unresponsive to one topical drug may respond to another and alternatives should be tried before considering more aggressive management. Topical drugs are often used in combination.

- Although effective, dithranol stains the skin and clothes and as it is irritant careful adjustment of the strength and duration of application needs to be made. It has traditionally been applied overnight in the form of ointments or pastes but newer short-contact regimens and creams are more suitable for home therapy.
- Coal tar is used either as crude extracts or refined products and although the refined products may be more aesthetically acceptable they may also be less effective.
- Salicylic acid enhances the rate of loss of surface scale and is included in many combination preparations with dithranol or coal tar.
- Calcipotriol and tacalcitol are vitamin D analogues, that have the advantage of being odourless and nonstaining. Maxacalcitol is another vitamin D analogue under investigation.
- Tazarotene, a retinoid, is also effective in psoriasis but significant irritation can limit its use and it should be avoided in pruritic psoriasis.
- Topical corticosteroids are also effective but they may lead to dermal atrophy, tachyphylaxis, systemic toxicity, and may precipitate unstable and pustular psoriasis. They are reported to be the most widely used treatment in the USA.[2]

Guttate psoriasis is strongly associated with streptococcal infection and patients may require antimicrobial treatment but firm evidence of a beneficial effect on the skin lesions[10] (or indeed of any intervention for guttate psoriasis[11]) is lacking.

Phototherapy with UVB light (290 to 320 nm) is effective when used alone for chronic plaque or guttate psoriasis but also enhances the efficacy of calcipotriol, coal tar, or dithranol. Studies have indicated that the therapeutic wavelengths are in the region of 311 to 313 nm. Consequently, narrowband UVB lamps (TL-01) have been developed to emit a spectrum that peaks at 311 nm.[12]

Photochemotherapy (PUVA) involves the use of oral or topical psoralens such as methoxsalen with UVA light and is generally considered to be the treatment of first choice for psoriasis that is resistant to topical therapies. Guidelines for PUVA have been published.[13,14] Psoralens have also been used with UVB light. Commercially available sunbeds, which emit UVA light, are not recommended as they are rarely effective and induce skin ageing and fragility.

Psoriasis refractory to topical therapy and PUVA may respond to **systemic drugs**. Systemic treatment may also be indicated for extensive chronic plaque psoriasis in elderly or infirm patients, for generalised pustular or erythrodermic psoriasis, or for severe psoriatic arthritis (see Spondyloarthropathies, p. 14.3).

- Immunosuppressants such as methotrexate are useful for severe refractory psoriasis, the aim of treatment being to bring psoriasis under control, enabling a return to other modes of treatment rather than to induce remission. Ciclosporin is also used in severe refractory psoriasis and may be used either to induce a remission or in low-dose maintenance therapy to prevent relapse. Tacrolimus, sirolimus, and mycophenolate are under investigation for both oral and topical use, and azathioprine has been tried.
- Systemic retinoids such as acitretin are also effective, and use with PUVA may allow a reduction in doses and associated toxicity for each therapy. Generalised pustular and palmoplantar pustular psoriasis are particularly responsive to acitretin. UVB therapy may also be used with acitretin.
- With the recognition that psoriasis is an auto-immune disease, immunomodulating drugs have been developed with an aim to provide selective immunotherapy, by either targeting T-cells or by cytokine modulation. Alefacept and efalizumab inhibit T-cell activation and show similar efficacy in the treatment of psoriasis. Cytokine modulating therapy includes blocking the action of tumour necrosis factor with adalimumab, etanercept, or infliximab, which have been found to be effective for psoriasis skin lesions and psoriatic arthritis. British[15] and American[16] guidelines endorse the use of biological treatments in appropriate patients.

  The British Association of Dermatologists recommends[15] that in chronic plaque psoriasis the biological therapies (adalimumab, etanercept, and infliximab) should be reserved for patients with severe disease that is unresponsive or refractory to standard therapies such as acitretin, ciclosporin, methotrexate, UVB, and PUVA, or when such therapies cannot be used. Adalimumab or etanercept are considered to be the first choice in stable disease. Adalimumab or infliximab may be useful when rapid disease control is needed; limited evidence suggests that infliximab may be first choice in unstable erythrodermic or generalised pustular psoriasis. Ustekinumab may also be used, but only if TNF therapy has failed or is contra-indicated. Also, it is worth considering a different TNF antagonist before trying ustekinumab. Methotrexate may be combined with either adalimumab, etanercept, or infliximab in certain circumstances e.g. associated arthropathy or to improve efficacy. American guidelines state that adalimumab, alefacept, or etanercept may be used in moderate to severe psoriasis but infliximab should be reserved for severe disease.[16] They also suggest the 3 cytokine modulators may be used in moderate to severe psoriatic arthritis and, like the British guidelines, support the combination of biological therapies with methotrexate in psoriatic arthritis.
- Hydroxycarbamide, fumarates, tioguanine, and sulfasalazine have also been tried. Many anecdotal reports note improvement of psoriasis when patients are given drug therapy for co-existing disease. The value of such drugs can be particularly difficult to establish because of the chronic relapsing and recurring nature of psoriasis.

The chronic nature of psoriasis has resulted in several different strategies being tried in order to maximise treatment efficacy and minimise toxicity.[5,6] Combinations of established drugs at lower doses can include methotrexate with either ciclosporin or acitretin, or acitretin with UV therapy. Sequential therapy uses a rapidly acting, potentially more toxic, drug to bring the condition under control initially, followed by a less toxic drug for maintenance; examples include using methotrexate or ciclosporin followed by acitretin. Rotational therapy may be used to minimise long-term toxicity by using each treatment for 1 to 2 years; methotrexate, acitretin, and UV therapy have been used in this way.[6] However, ciclosporin should not follow PUVA therapy in this way because of an increased risk of cutaneous squamous cell carcinoma.[5] There is limited experience with the use of newer immunomodulating drugs in these regimens.[6]

1. Griffiths CEM, *et al.* A systematic review of treatments for severe psoriasis. *Health Technol Assess* 2000; 4: 1–125. Also available at: http://www.hta.ac.uk/fullmono/mon440.pdf (accessed 20/07/10)
2. Lebwohl M. Psoriasis. *Lancet* 2003; 361: 1197–1204.
3. Naldi L, Griffiths CEM. Traditional therapies in the management of moderate to severe chronic plaque psoriasis: an assessment of the benefits and risks. *Br J Dermatol* 2005; 152: 597–615.
4. van de Kerkhof PCM, Kragballe K. Recommendations for the topical treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2005; 19: 495–9.
5. Fairhurst DA, *et al.* Optimal management of severe plaque form of psoriasis. *Am J Clin Dermatol* 2005; 6: 283–94.
6. Cather JC, Menter A. Combining traditional agents and biologics for the treatment of psoriasis. *Semin Cutan Med Surg* 2005; 24: 37–45.
7. British Association of Dermatologists. Psoriasis – general management. Available at: http://www.bad.org.uk/site/769/Default.aspx (accessed 25/05/10)
8. Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. *Lancet* 2007; 370: 263–71.
9. Menter A, Griffiths CEM. Current and future management of psoriasis. *Lancet* 2007; 370: 272–84.
10. Owen CM, *et al.* Antistreptococcal interventions for guttate and chronic plaque psoriasis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2000 (accessed 25/09/07).
11. Chalmers RJG, *et al.* Interventions for guttate psoriasis. Available in The Cochrane Database of Systematic Reviews: Issue 2. Chichester: John Wiley; 2000 (accessed 25/09/07).
12. Ibbotson SH, *et al.* British Association of Dermatologists. An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *Br J Dermatol* 2004; 15 : 283–97. Also available at: http://www.bpg.org.uk/publications/report/1.pdf (accessed 25/05/10)
13. British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; 130: 246–55.
14. Halpern SM, *et al.* Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; 142: 22–3 . Also available at: http://www.bad.org.uk/Portals/_Bad/Guideline/Clinical%20Guidelines/Topical%20PUVA%20Therapy.pdf (accessed 25/05/10)
15. Smith CH, *et al.* British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; 161: 987–1019. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Biologics%20guidelines%202009.pdf (accessed 25/05/10)
16. Menter A, *et al.* American Academy of Dermatology. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 2. overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 2008; 58: 826–50. Also available at: http://www.aad.org/research/_doc/Psosection1.pdf (accessed 25/05/10)

Pyoderma gangrenosum

Pyoderma gangrenosum is a rare serious ulcerative skin disorder often associated with systemic diseases such as inflammatory bowel disease, rheumatoid arthritis, or myeloproliferative disorders. Initially an acutely inflamed nodule is present which progresses very rapidly to large painful ulcers. Any area of the body may be involved, but the face, legs, and buttocks are frequent sites.

Treatment essentially consists of cleansing and dressing for the ulcers and appropriate therapy for any underlying disease. When necessary high doses of systemic corticosteroids or treatment with ciclosporin may be given. There have also been reports in small numbers of patients of benefit with sulfasalazine, dapsone, azathioprine, tacrolimus, thalidomide, infliximab, colchicine, and nicotine chewing gum.

A related but less severe form of the disease, superficial granulomatous pyoderma, has responded to intralesional or oral corticosteroids.

General references.
1. Callen JP. Pyoderma gangrenosum. *Lancet* 1998; 351: 581–5.
2. Reichrath J, *et al.* Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. *J Am Acad Dermatol* 2005; 53: 273–83.
3. Campbell S, *et al.* Therapy insight: pyoderma gangrenosum—old disease new management. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 587–94.
4. Brooklyn T, *et al.* Diagnosis and treatment of pyoderma gangrenosum *BMJ* 2006; 333: 181–4.
5. Ruocco E, *et al.* Pyoderma gangrenosum: an updated review. *J Eur Acad Dermatol Venereol* 2009; 23: 1008–17.
6. Miller J, *et al.* Pyoderma gangrenosum: a review and update on new therapies. *J Am Acad Dermatol* 2010; 62: 646–54.

Rosacea

Rosacea is a chronic condition affecting the face; rarely, the trunk and limbs may be affected. Phases of this disorder include flushing episodes, persistent erythema and telangiectasia, an inflammatory papulopustular phase, and in advanced cases rhinophyma (nasal hypertrophy and deformity). Ocular involvement is also common and can cause conjunctivitis, keratitis, styes, and chalazia.[1-4] The precise cause of rosacea remains unclear. It has been suggested that *Helicobacter pylori* in the gastrointestinal tract may cause flushing by inducing the production of endogenous vasodilators, and that *Demodex folliculorum*, a mite found in human follicles, may have a role in papulopustular rosacea.[3]

The inflammatory episodes of rosacea (papules, swelling, and pustules) are responsive to treatment, but the underlying erythema and telangiectasia usually persist.

- Episodes of flushing may be limited by avoiding trigger factors such as alcoholic and hot drinks, and spicy foods.[1,4,5] Patients should use soap-free cleansers and high factor sunscreens.[1,3] In severe cases clonidine or a beta blocker such as atenolol, has been used.[3]
- Persistent erythema may be improved by *H. pylori* eradication (see Peptic Ulcer Disease, p. 1813.2) but the efficacy of such therapy has not been established.[3]
- Papulopustular rosacea is usually controlled effectively by oral antibacterials.[1,3-6] Tetracyclines (doxycycline, minocycline, oxytetracycline, tetracycline) have been widely used, but clarithromycin, erythromycin, and metronidazole are suitable alternatives. Improvement occurs over several weeks, and long-term treatment may be necessary. Systemic isotretinoin is also effective, but it is generally reserved for severe or resistant cases of rosacea.

  Topical therapies, particularly metronidazole and azelaic acid,[3-5,7,8] provide effective alternatives to oral drugs. Other topical therapies that may be useful include tetracyclines, clindamycin, erythromycin, retinoids, or a combination of sulfacetamide sodium with sulfur. Where infestations of *D. folliculorum* are suspected of aggravating the condition, topical treatments such as benzyl

benzoate, crotamiton, or permethrin may be tried. There are also anecdotal reports of the successful treatment of demodicidosis with oral ivermectin. Topical corticosteroids should not be used because they exacerbate rosacea.

- Ocular rosacea symptoms are managed with eyelid hygiene and artificial tears. Metronidazole gel can be applied to the eyelids but systemic antibacterials may be needed for more severe disease.[4,5]
- Rhinophyma requires conventional or laser surgery;[1,3-5] isotretinoin may be used for a few months preoperatively to shrink the bulbous portions.[1]

Non-drug therapies that have been advocated include facial massage;[1] however, as for many of the drug therapies[7] controlled studies are lacking. Laser therapy has been used to obliterate telangiectasia.[1,3,5]

1. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med* 1997; 90: 144–50.
2. Wilkin J, *et al.* Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol* 2002; 46: 584–7. Also available at: http://www.rosacea.org/class/classsystem.php (accessed 26/09/07)
3. Rebora A. The management of rosacea. *Am J Clin Dermatol* 2002; 3: 489–96.
4. Powell FC. Rosacea. *N Engl J Med* 2005; 352: 793–803.
5. Gupta AK, Chaudhry MM. Rosacea and its management: an overview. *J Eur Acad Dermatol Venereol* 2005; 19: 273–85.
6. Baldwin HE. Oral therapy for rosacea. *J Drugs Dermatol* 2006; 5: 16–21.
7. van Zuuren EJ, *et al.* Interventions for rosacea. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 26/09/07).
8. Nally JB, Berson DS. Topical therapies for rosacea. *J Drugs Dermatol* 2006; 5: 23–6.

Seborrhoeic dermatitis

Seborrhoeic dermatitis is a common eczematous skin disorder (see Eczema p. 1684.1) in which erythematous pruritic patches of skin may become either scaly or exudative and crusted. Scaling lesions are the type most commonly seen. In some cases, known as seborrhoeic folliculitis, there may also be follicular papules or pustules. Seborrhoeic dermatitis occurs in regions of the body where sebaceous glands are plentiful, such as the scalp, face, and chest, although the condition is not associated with increased sebum production. The cause of seborrhoeic dermatitis is unknown, although it might be related to overgrowth with *Malassezia ovalis* (*Pityrosporum ovale*), a normal commensal yeast.

Treatment is suppressive rather than curative. Topical preparations containing antifungals such as ciclopirox olamine, terbinafine, or an imidazole (bifonazole, ketoconazole, miconazole), usually with hydrocortisone, are the main drugs used. If unsuccessful, keratolytics such as salicylic acid or tars may be used. Topical macrolactam immunosuppressants such as pimecrolimus and tacrolimus are being investigated as alternate therapy. Shampoos containing ketoconazole, pyrithione zinc, or selenium sulfide are commonly used for scalp involvement. Topical lithium succinate has been tried.

Dandruff due to normal shedding of scalp skin (pityriasis capitis) is treated similarly to seborrhoeic dermatitis of the scalp.

Reviews.

1. Gupta AK, Bluhm R. Seborrheic dermatitis. *J Eur Acad Dermatol Venereol* 2004; 18: 13–26.
2. Naldi L, Rebora A. Seborrheic dermatitis. *N Engl J Med* 2009; 360: 387–96.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (Lyell's syndrome or scalded skin syndrome) is usually a drug-induced skin reaction. It has been described as a severe form of Stevens-Johnson syndrome, or as the most severe form of erythema multiforme (p. 1684.3), although such classifications have been debated. It generally begins with lesions of the mucous membranes of the oropharynx, eyes, and genitalia, and fever and pain. Subsequently, a macular rash, blisters, or diffuse erythema develop, and affected skin may detach irregularly, sometimes in large sheets. Toxic epidermal necrolysis is managed similarly to burns (p. 1683.1), but specific treatments have not been established. The use of systemic corticosteroids is controversial because of a higher risk of infection. Other treatments that have been tried with some reports of benefit include plasmapheresis, intravenous immunoglobulin, cyclophosphamide, ciclosporin, and infliximab.

References.

1. Becker DS. Toxic epidermal necrolysis. *Lancet* 1998; 351: 1417–20.
2. Spies M, *et al.* Treatment of extensive toxic epidermal necrolysis in children. *Pediatrica* 2001; 108: 1162–8.
3. Fischer M, *et al.* Antitumour necrosis factor-α antibodies (infliximab) in the treatment of a patient with toxic epidermal necrolysis. *Br J Dermatol* 2002; 146: 707–8.
4. Majumdar S, *et al.* Interventions for toxic epidermal necrolysis. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 26/09/07).
5. Faye O, Roujeau J-C. Treatment of epidermal necrolysis with high-dose intravenous immunoglobulins (IVIg): clinical experience to date. *Drugs* 2005; 65: 2085–90.
6. Chave TA, *et al.* Toxic epidermal necrolysis: current evidence, practical management and future directions. *Br J Dermatol* 2005; 153: 241–53.
7. Hunger RE, *et al.* Rapid resolution of toxic epidermal necrolysis with anti-TNF-α treatment. *J Allergy Clin Immunol* 2005; 116: 923–4.
8. Abood GJ, *et al.* Treatment strategies in toxic epidermal necrolysis syndrome: where are we at? *J Burn Care Res* 2008; 29: 269–76.

Urticaria and angioedema

Urticaria and angioedema are conditions caused by the release of inflammatory mediators from mast cells and basophils. **Urticaria** (also known as nettlerash or hives) is characterised by circumscribed, elevated, erythematous, and usually pruritic areas of oedema (wheals) involving the superficial portion of the dermis. Individual lesions arise suddenly, often within a few minutes, and may last up to 24 hours. In severe, acute urticaria, wheals may cover most of the skin surface. In chronic urticaria (continuous or recurrent lesions over at least 6 weeks) only a few wheals may develop each day. When subcutaneous or submucosal tissues are involved, causing swelling of the eyelids, lips, tongue, larynx, or genitalia, the condition is called **angioedema**. For hereditary angioedema, caused by complement C1 esterase inhibitor deficiency, see p. 2485.2.

Although urticaria may be caused by an allergy, it often has a non-allergic mechanism. Urticaria occurs as an adverse effect of many drugs, for example aspirin and many antibacterials. Other types of urticaria include dermographism (linear wheal formation on scratching or stroking) and cholinergic urticaria (evoked by such triggers as exercise, heat, and emotion and characterised by small papulous wheals surrounded by an erythematous flare). In **idiopathic anaphylaxis**, patients have attacks of urticaria or angioedema, sometimes with bronchospasm, hypotension, or syncope.

The **management** of urticaria and angioedema has been reviewed.[1-5] Avoidance of unnecessary exposure to known allergens or triggers is of prime importance in the management of urticaria, although in many chronic cases no trigger factor can be found. Severe, acute urticaria or angioedema requires urgent treatment as for anaphylaxis (p. 1293.2).

- Topical treatment of urticaria is rarely effective except for mild cases. Calamine, menthol, and crotamiton have cooling or antipruritic effects. Topical corticosteroids are of no value; topical antihistamines are not very effective and carry a slight risk of sensitisation.
- Most patients with urticaria derive some benefit from oral antihistamines (H_1-antagonists), especially in the relief of pruritus. A non-sedating antihistamine is the first line of treatment. If necessary, the dose may be increased after a few weeks or a different non-sedating antihistamine may be used. Combination with a leukotriene antagonist (see below) may also be tried.[4,5]
- Leukotriene antagonists such as montelukast and zafirlukast and the leukotriene inhibitor zileuton have been used alone and with antihistamines in the management of urticaria. Montelukast may add benefit to an antihistamine in chronic urticaria associated with hypersensitivity to aspirin or food additives, and in patients with evidence of histamine-releasing autoantibodies, but not in chronic idiopathic urticaria. There is some anecdotal evidence that antileukotrienes might be useful in primary cold urticaria, delayed pressure urticaria, and dermographism.[6]
- A short course of an oral corticosteroid may be indicated for control of acute urticaria in patients refractory to other measures.
- Severe disease difficult to treat with non-sedating antihistamines may respond to a combination with ciclosporin;[4,5] alternatively, omalizumab or dapsone may be considered in certain patients.[5] The combination of non-sedating antihistamines with H_2-antagonists such as ranitidine is sometimes used. However, some[5] consider this to be supported by weak evidence. Similarly, the use of drugs such as doxepin, which has H_1- and H_2-antagonist properties, and the calcium-channel blocker nifedipine, is based on weak evidence.[5] Although sedating antihistamines may be useful at bedtime, their use has been discouraged mainly because of the associated adverse effects.
- Addition of a sympathomimetic such as terbutaline has also been suggested for patients unresponsive to treatment with an H_1-antagonist alone, but results have varied.

It has been suggested that chronic urticaria may be associated with thyroid auto-immunity and that levothyroxine therapy may be of benefit in patients with antithyroid antibodies. Several other drugs including danazol, stanozolol, sulfasalazine, and intravenous immunoglobulin have reportedly produced benefit in limited numbers of patients, but such therapies are largely used empirically.

Patients with frequent attacks of idiopathic anaphylaxis have benefited from prophylaxis with a corticosteroid and antihistamine; once the condition is controlled the corticosteroid, and then the antihistamine, may be tapered and gradually withdrawn. Adjuvant ketotifen, cromoglicate, salbutamol, or montelukast may be helpful in permitting corticosteroid tapering in dependent patients. Adrenaline should be available for acute attacks.[7]

1. Kaplan AP. Chronic urticaria and angioedema. *N Engl J Med* 2002; 346: 175–9.
2. Kozel MMA, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs* 2004; 64: 2515–36.
3. Grattan CEH, Humphreys F. British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Guidelines for evaluation and management of urticaria in adults and children. *Br J Dermatol* 2007; 157: 1116–23. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Urticaria%20and%20Angiodema%20(2007).pdf (accessed 25/05/10)
4. Komarow HD, Metcalfe DD. Office-based management of urticaria. *Am J Med* 2008; 121: 379–84.
5. Zuberbier T, *et al.* EAACI/GA²LEN/EDF/WAO guideline: management of urticaria. *Allergy* 2009; 64: 1427–43. Also available at: http://www.euroderm.org/download/guideline_update-eaaci_ga_2_len_edf_wao_guideline_management_of_urticaria.pdf (accessed 13/11/09)
6. Di Lorenzo G, *et al.* Is there a role for antileukotrienes in urticaria? *Clin Exp Dermatol* 2006; 31: 327–34.
7. Lenchner K, Grammer LC. A current review of idiopathic anaphylaxis. *Curr Opin Allergy Clin Immunol* 2003; 3: 305–11.

Warts

Warts are caused by human papillomaviruses. The lesions present in several different forms and can affect any skin site although the hands, feet, and anogenital areas are most frequently affected. Plantar warts on the soles of the feet are sometimes called verrucas. Anogenital warts are known as condylomata acuminata. Warts do disappear spontaneously but as they may not do so for months or years patients often seek treatment.

There is no specific antiviral therapy against the human papillomavirus,[1-6] although cidofovir has been tried (see below). Treatment usually relies on some form of local tissue destruction.

- Non-pharmacological techniques include surgical excision, electrocauterisation, or laser therapy. Photodynamic therapy using 5-aminolevulinic acid is also a possible treatment option.[7] Cryotherapy (tissue freezing) may be performed with liquid nitrogen or solid carbon dioxide.
- Chemical destruction with acids (acetic acid, lactic acid, nitric acid, salicylic acid, or trichloroacetic acid), silver nitrate, formaldehyde or glutaral, or podophyllum resin or its derivatives (podophyllotoxin) is another option. Podophyllum resin and podophyllotoxin are often used for anogenital warts.
- Intralesional injection of cytotoxics such as bleomycin or fluorouracil also destroys the wart and may be used in severe or resistant cases. Fluorouracil may also be applied topically.

Other treatments based on less destructive mechanisms have also been used.

- Tretinoin has been tried topically for its effect on epidermal growth.
- Imiquimod is an immune response modifier that is used topically to treat anogenital warts. There is also some evidence to suggest that it is effective for other cutaneous warts. Other drugs with immunomodulatory effects, such as cimetidine, have been tried in a few patients. There are also small studies of treatment with diphencyprone, a contact sensitiser.
- Interferons have antiviral, antiproliferative, and immunomodulatory actions and have thus been investigated in the management of warts; some studies, especially those involving intralesional administration, have showed benefit. Other routes of administration are under investigation; topical interferon alfa for anogenital warts, and an oral formulation for warts in the oral cavity of patients with HIV infection.
- Cidofovir is an antiviral that has activity against human papillomavirus. Investigational intravenous or topical use has been successful in a small number of patients with cutaneous or anogenital warts.
- Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, it is used in the treatment of external genital and perianal warts.

A quadrivalent recombinant human papillomavirus vaccine has recently been developed and is used to prevent anogenital warts, cervical cancer, and other pre-cancerous lesions caused by human papillomavirus types 6, 11, 16, and 18.

1. Sterling JC, *et al.* British Association of Dermatologists. Guidelines for the management of cutaneous warts. *Br J Dermatol* 2001; 144: 4–11. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Cutaneous%20Warts.pdf (accessed 25/05/10)
2. von Krogh G, *et al.* European Course on HPV Associated Pathology (ECHPV). European guideline for the management of anogenital warts. *Int J STD AIDS* 2001; 12 (suppl 3): 40–7. Also available at: http://www.luxi.org/sti-information/pdf/guidelines.pdf (accessed 26/09/07)
3. Micali G, *et al.* Management of cutaneous warts: an evidence-based approach. *Am J Clin Dermatol* 2004; 5: 311–17.
4. Bellew SG, *et al.* Childhood warts: an update. *Cutis* 2004; 73: 379–84.
5. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 26/09/07).
6. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; 59 (RR-12): 1–110. Correction. *ibid.* 2011; 60: 18. [dose] Also

available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 02/02/11)
7. Morton CA, *et al.* British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group. Guidelines for topical photodynamic therapy: update. *Br J Dermatol* 2008; 159: 1245–66. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/PDTguideline%20BJD%20Dec%202008.pdf (accessed 25/05/10)

Wounds and ulcers

Wounds (physical injuries of the skin and underlying structures) may be the result of mechanical trauma, burns, or chemical injury. Ulcers are often the result of various underlying disorders. Among the commonest types, *decubitus ulcers* (bedsores, pressure sores) occur in patients with extended immobility when prolonged pressure on the skin over a bony prominence produces localised ischaemia. *Leg ulcers* may result from venous incompetence (venous ulcers) or be ischaemic in origin (arterial ulcers), while patients with peripheral neuropathy, such as diabetics or those with leprosy, may develop *neuropathic ulcers* due to repetitive inadvertent injury. Wounds or ulcers may be described as superficial, partial thickness, or full thickness. Superficial wounds are limited to epithelial tissue and heal rapidly by regeneration of epithelial cells. Partial thickness wounds involve the dermis and include some blood vessel damage, and therefore wound repair is a longer process. Full thickness wounds extend at least to subcutaneous fat, and healing requires synthesis of new connective tissue.

Healing mechanisms are essentially the same regardless of the cause of the damage:

- immediate haemostatic processes involve formation of a platelet plug and fibrin clot, as described under Haemostasis and Fibrinolysis, p. 1124.3
- the early granulation and re-epithelialisation phase takes place up to about 21 days after injury depending on wound size and site. Platelet-derived growth factors stimulate fibroblasts to produce granulation tissue, comprising a collagen matrix well-supplied with capillary vessels, and growth of epidermal cells leading to re-epithelialisation of the wound surface
- during the final dermal repair and remodelling phase the collagen matrix undergoes strengthening and there is a reduction in vascularity. This phase can continue for up to 2 years after injury.

Several factors are important for efficient wound healing. Adequate supplies of nutrients, especially vitamin C and zinc (which are often given as supplements) and oxygen are needed. A good blood supply is thus essential. Clinical infection, either systemic or local, due to contamination by environmental microbes, causes tissue damage and delays healing. The process of wound repair requires many cellular and acellular factors, such as platelets and growth factors, and deficiencies in these may also be responsible for delayed healing. Thus, the patient's age, systemic conditions, concomitant drugs, nutritional status, and congenital deficiencies all influence the rate of healing.

Local **wound management** includes cleansing, removal of exudate, and prevention of microbial contamination. Choice of wound treatment preparation will depend on the size, location, type, and cause of the wound, on the presence of infection, and on the particular stage of healing.

Wound **cleansing** is required to remove any dirt or foreign bodies and to **remove exudate** and slough (pus and necrotic tissue). This helps to prevent infection and aids healing. Commonly used cleansing solutions are sodium chloride 0.9%, hypochlorite, hydrogen peroxide, povidone-iodine, and chlorhexidine. However, some antiseptics and hypochlorites might be associated with delayed wound healing, especially with prolonged use, as they delay collagen production and cause inflammation. Also, many antiseptics are inactivated by organic material. Sodium chloride solution may be all that is required for routine cleansing of non-infected wounds.

Many of the cleansing solutions also help to remove slough. Other wound management preparations more specifically directed at removing slough include dextranomer, hydrogels, hydrocolloids, and enzyme preparations such as a mixture of streptokinase and streptodornase. Dextranomer, hydrogels, and hydrocolloids cause debridement by their occlusive, rehydrating properties. Surgical debridement is a fast and efficient way of removing necrotic tissue. Larval therapy (the use of live sterile maggots of *Lucilia sericata*, the common greenbottle fly) has also been effective for debridement of infected or necrotic wounds, including diabetic foot ulceration.

Wounds may produce large volumes of exudate as a result of inflammatory reactions, especially during the first few days. Hydrocolloid and alginate preparations and foam dressings are effective moisture absorbers.

All wounds are colonised by bacteria to some extent and there is no evidence that this superficial **infection** affects healing. However, infection with *Pseudomonas aeruginosa* may delay healing. Topical antimicrobials may be considered, but short-term use is advisable; sulfadiazine silver is used, especially in burns. Acetic acid has also been used. Infections are treated systemically if there are indications of clinical infection such as sudden pain, cellulitis, and increased discharge; systemic management of bacterial skin infections is described on p. 207.1.

Wound **dressings** and packing preparations help to protect the wound and provide the correct environment for wound healing. Some also help by absorbing exudate. Superficial wounds usually only require a low-adherent dressing. Traditional dry dressings such as cotton wool, gauze, and lint are not used for partial or full thickness cavity wounds since they shed fibres, adhere to the wound, and cause wound dehydration. Hydrogels, hydrocolloids, polysaccharides, cadexomer-iodine, alginates, and foam dressings are all effective cavity wound preparations. Hyaluronic acid is incorporated into some dressings to promote wound healing.

Activated charcoal is very effective at reducing offensive odours from **malodorous wounds**, as are sugar (sucrose) pastes. Sucrose may exert its antibacterial effect by competing for water present in the cells of bacteria. Metronidazole is active against anaerobic bacteria that are associated with the pungent smell and is used topically for deodorising malodorous tumours. Metronidazole is not generally used on wounds because of the risk of inducing resistance but it is sometimes used to deodorise malodorous venous leg ulcers or decubitus ulcers.

In addition to the use of wound preparations, there may be other measures that aid healing of specific wounds or ulcers. Some wounds may require skin grafting. Skin substitutes, and growth factors, such as becaplermin, molgramostim, trafermin, and urogastrone, are being used or developed for non-healing ulcers and wounds. Autologous blood-derived platelet gels containing growth factors are available to aid and accelerate wound healing. Topical phenytoin has produced some encouraging results in promoting the healing of various types of ulcers. Measures that aid the return of fluid from the leg, such as flexing the ankles, elevation, and use of compression bandages are beneficial in **venous ulcers**. There is insufficient evidence to recommend one type of dressing in preference to another, including the use of hydrocolloid dressings instead of simple low adherent dressings. The bioflavonoids, given orally, may improve venous insufficiency and therefore also aid healing. Systemic drugs that improve the supply of oxygen to tissues, for example pentoxifylline, may be useful in ischaemic and venous ulcers. Topical and systemic ketanserin has been investigated in a few patients and may be beneficial in wounds and ulcers where there is impaired blood flow. Hyperbaric oxygen therapy has been tried in a range of chronic wounds; it might be useful in reducing amputation in patients with chronic diabetic foot ulcers. Vascular surgery may be necessary in the management of some ulcers caused by ischaemia or chronic venous insufficiency. In **decubitus ulcers**, relief of pressure is the most important measure in management. Support surfaces and the use of various products containing silicone may help protect fragile tissue. The management of **burns** and **chemical burns** is described on p. 1683.1.

General references.

1. Douglas WS, Simpson NB. Guidelines for the management of chronic venous leg ulceration: report of a multidisciplinary workshop. *Br J Dermatol* 1995; 132: 446–52.
2. Smith DM. Pressure ulcers in the nursing home. *Ann Intern Med* 1995; 123: 433–42.
3. Grey JE, Harding KG. The chronic non-healing wound: how to make it better. *Hosp Med* 1998; 59: 557–63.
4. Orlando PL. Pressure ulcer management in the geriatric patient. *Ann Pharmacother* 1998; 32: 1221–7.
5. Singer AJ, Clark RAF. Cutaneous wound healing. *N Engl J Med* 1999; 341: 738–46.
6. Morgan DA. Wound management products in the drug tariff. *Pharm J* 1999; 263: 820–5.
7. London NJM, Donnelly R. ABC of arterial and venous disease: ulcerated lower limb. *BMJ* 2000; 320: 1589–91.
8. Harding KG, *et al.* Healing chronic wounds. *BMJ* 2002; 324: 160–3.
9. de Araujo T, *et al.* Managing the patient with venous ulcers. *Ann Intern Med* 2003; 138: 326–34.
10. Anonymous. Leg ulcers. In: Buxton PK, ed. *ABC of Dermatology*. 4th ed. London: BMJ Publishing Group, 2003: 43–6.
11. European Pressure Ulcer Advisory Panel. Nutritional guidelines for pressure ulcer prevention and treatment (issued 16th November, 2003). Available at: http://www.epuap.org/guidelines/english_nutritional_guidelines.pdf (accessed 27/09/07)
12. Cannon BC, Cannon JP. Management of pressure ulcers. *Am J Health-Syst Pharm* 2004; 61: 1895–1905.
13. Simon DA, *et al.* Management of venous leg ulcers. *BMJ* 2004; 328: 1358–62.
14. Enoch S, *et al.* ABC of wound healing: non-surgical and drug treatments. *BMJ* 2006; 332: 900–903.
15. Reddy M, *et al.* Preventing pressure ulcers: a systematic review. *JAMA* 2006; 296: 974–84.
16. Vowden KR, Vowden P. Preventing venous ulcer recurrence: a review. *Int Wound J* 2006; 3: 11–21.
17. Palfreyman S, *et al.* Dressings for venous leg ulcers: systematic review and meta-analysis. *BMJ* 2007; 335: 244–8.
18. Reddy M, *et al.* Treatment of pressure ulcers: a systematic review. *JAMA* 2008; 300: 2647–62.
19. European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel. Pressure ulcer treatment: quick reference guide (issued 2009). Available at: http://www.epuap.org/guidelines/Final_Quick_Treatment.pdf (accessed 17/12/09)

Abrasive Agents

Abrasivos; Абразивные Вещества; Шлифовальные Средства.

Aluminium Oxide

Aliuminio oksidas; Alumiinioksidi; Aluminii Oxidum; Aluminio, óxido de; Aluminiumoxid; Aluminium-oxid; Aluminium Oxide; Glinu tlenek; Алюминия Оксид.

Al_2O_3=102.0

CAS — 1344-28-1.

ATC — D10AX04.

ATC Vet — QD10AX04.

UNII — LMI26O6933.

Pharmacopoeias. In *USNF*.

Eur. (see p. vii) includes the hydrated form (see Aluminium Hydroxide, p. 1817.2).

USNF 31: (Aluminum Oxide). It contains not less than 47.0% and not more than 60.0% of Al_2O_3. A white or almost white, amorphous powder. Practically insoluble in water; very slightly soluble in dilute mineral acids and in solutions of alkali hydroxides. Store in airtight containers. at a temperature not exceeding 30 degrees.

Pumice

Lapis Pumicis; Piedra pómez; Pierre Ponce Granulée; Pumex; Pumex Granulatus; Pumice Stone; Пемза.

CAS — 1332-09-8.

Pharmacopoeias. In *US*.

USP 36: (Pumice). Pumice is a substance of volcanic origin consisting chiefly of complex silicates of aluminium, potassium, and sodium. Odourless, very light, hard, rough, porous greyish masses or gritty, greyish powder. It is stable in air. Practically insoluble in water and not attacked by acids. Three grades of powdered pumice are recognised:

- superfine (=pumice flour)—not less than 97% passes through a No. 200 [US] sieve
- fine—not less than 95% passes through a No. 150 sieve and not more than 75% through a No. 200 sieve
- coarse—not less than 95% passes through a No. 60 sieve and not more than 5% through a No. 200 sieve

Profile

Abrasive agents such as fused synthetic aluminium oxide or powdered pumice have been used either as adjuncts in the treatment of acne (despite doubts about their value—see p. 1682.2) or for the removal of hard skin. Pumice has also been used as a dental abrasive and as a filtering medium. Other agents used as abrasives for acne include polyethylene granules.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Abralux: Ionax Scrub: Puracilin Exfoliante; *Austral.*: Brasivol†; *Braz.*: Ionax Scrub; *Chile*: Ionax Scrub; Podexine Exfoliante; Scrub-Atlas; *Fr.*: Brasivol; *Irl.*: Brasivol†; *Malaysia*: Ionax Scrub; *Mex.*: Betagranulos; Ionax Scrub; *Philipp.*: Ionax Scrub; *S.Afr.*: Brasivol†; *Singapore*: Ionax Scrub; *UK*: Brasivol; *USA*: Brasivol; Ionax Scrub; *Venez.*: Betagranulos; Ionax Scrub.

Multi-ingredient Preparations. *Arg.*: Scrub-Atlas; *Belg.*: Stomacid; *Chile*: Podexine Durezas y Callosidades; *Hung.*: Gastracid; *Indon.*: Aludonna; *Ital.*: Clarifex Scrub; *Mex.*: Dermobras; *S.Afr.*: Pedimed†; *Switz.*: Cliniderm; *Ukr.*: Altacid (Алтацид)†; *USA*: Pernox; Zanfel; *Venez.*: Exfoliderm.

Homoeopathic Preparations. *Canad.*: Comp-Drops 3 Bowel Support†; Eczema; Headache & Migraine; Homeo-Form CO†; Homeo-Form MI†; Reneel†; *Ger.*: Curare comp; Gastriselect N; Infifer N; Lowe-Komplex Nr 6; *Neth.*: Colintest-Gastreu R37; Enulite; Gynaelite; *Switz.*: Gastronol; Regenaplex Nr 38b.

Acitretin *(BAN, USAN, rINN)*

Acitretina; Acitretinas; Acitrétine; Acitretinum; Asitretiini; Asitretin; Etretin; Etretina; Ro-10-1670; Ro-10-1670/000; Ацитретин.

(*all-trans*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid; (2*E*,4*E*,6*E*,8*E*)-9-(4-Methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetraenoic acid.

$C_{21}H_{26}O_3$=326.4

CAS — 55079-83-9.

ATC — D05BB02.

ATC Vet — QD05BB02
UNII — LCH760E9T7.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Acitretin). A yellow or greenish-yellow, crystalline powder. It shows polymorphism. Practically insoluble in water; slightly soluble in alcohol and in acetone; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. It is sensitive to air, heat, and light, especially in solution. Store at 2 degrees to 8 degrees in airtight containers. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and any unused part be protected by an atmosphere of inert gas.

USP 36: (Acitretin). A yellow or greenish, crystalline powder. Practically insoluble in water; slightly soluble in acetone and in alcohol; very slightly soluble in cyclohexane; sparingly soluble in tetrahydrofuran. Store in airtight containers at 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light.

Uses and Administration

Acitretin is a retinoid and is a metabolite of etretinate (p. 1703.3). It is used orally in the treatment of severe psoriasis resistant to other forms of therapy, palmo-plantar pustular psoriasis, severe congenital ichthyosis and Darier's disease (keratosis follicularis), and in severe lichen planus.

In the UK, acitretin is given in an initial daily dose of 25 or 30 mg with food for 2 to 4 weeks; in the USA (where it is licensed only for use in psoriasis) initial doses up to 50 mg daily are permitted. The daily dosage is adjusted thereafter according to clinical response and adverse effects; optimal results are usually obtained with 25 to 50 mg given daily for a further 6 to 8 weeks but some patients may require up to 75 mg daily. For the treatment of Darier's disease a starting dose of 10 mg may be appropriate, adjusted thereafter according to response. In Darier's disease and congenital ichthyosis treatment may be required for more than 3 months but a daily dosage of 50 mg should not be exceeded. In the UK, licensed product information recommends that continuous treatment should not last longer than 6 months for any indication because of limited clinical data. For lichen planus, doses are similar to those used in the UK (see above).

For doses in children, see below.

Administration in children. Acitretin is not generally considered suitable for use in children. However, reviews[1,2] of its use in children with severe inherited disorders of keratinisation reported that acitretin was an effective and safe treatment provided that the minimal effective dose was used and that adverse effects were carefully monitored. UK licensed product information contra-indicates acitretin use in children unless the benefits significantly outweigh the risks, particularly premature epiphyseal closure and other skeletal effects associated with retinoids. However, if deemed necessary an oral dose of 500 micrograms/kg once daily (occasionally up to 1 mg/kg daily for limited periods) has been suggested, but the maximum daily dose should not exceed 35 mg. The *BNFC* suggests that these doses may be used under expert supervision for children aged 1 month to 12 years for the treatment of severe extensive psoriasis resistant to other forms of therapy, palmo-plantar pustular psoriasis, severe congenital ichthyosis, and Darier's disease. The adult dose (see above) is considered suitable for children from 12 years of age. The *BNFC* also includes a dose of 500 micrograms/kg daily (occasionally up to 1 mg/kg daily) for the management of harlequin ichthyosis in neonates.

1. Lacour M, *et al.* An appraisal of acitretin therapy in children with inherited disorders of keratinization. *Br J Dermatol* 1996; 134: 1023–9.
2. Zhang X-B, *et al.* Clinical investigation of acitretin in children with severe inherited keratinization disorders in China. *J Dermatolog Treat* 2008; 19: 221–8.

Eye disorders. A case report indicated that acitretin, given for psoriasis at an initial dose of 30 mg daily for one month and then reduced to 20 mg daily, improved corneal opacities in a patient with chronic tuberculosis-related interstitial keratitis.[1]

1. Labetoulle M, *et al.* Rapid improvement of chronic interstitial keratitis with acitretin. *Br J Ophthalmol* 2002; 86: 1445–6.

Malignant neoplasms. Acitretin may be useful in preventing the development of skin neoplasms in high-risk individuals, such as solid organ transplant recipients.[1,2] However, long-term therapy is needed to maintain the effect and adverse effects can limit its use[2] (see also Malignant Neoplasms under Isotretinoin, p. 1707.1). Gradual dose escalation may help to minimise mucocutaneous effects, and one proposed schedule for oral acitretin starts with 10 mg on alternate days for 2 weeks, 10 mg daily for the next 2 weeks, then 20 mg daily for a month; the dose is then adjusted as tolerated. Maintenance regimens of 25 mg daily, or alternating daily doses of 10 mg and 20 mg, have been used.[3]

1. Chen K, *et al.* Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; 152: 518–23.
2. Kovach BT, *et al.* Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; 19: 726–34.
3. Otley CC, *et al.* Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; 32: 562–8.

Skin disorders. Acitretin is used alone or with PUVA (a psoralen with UVA irradiation, see p. 1712.1) or UVB in psoriasis[1-5] (p. 1688.1). Studies have shown that use with PUVA or UVB light may increase efficacy and allow a reduction in the exposure to radiation required. It is also used in keratinisation disorders such as severe forms of ichthyosis[1,5-8] (p. 1685.1) and Darier's disease (keratosis follicularis)[1,5,9] (p. 1683.2). Benefit has been reported in various other skin disorders including lichen planus (p. 1685.2), lichen sclerosus (p. 1685.2), and cutaneous lupus erythematosus (p. 1613.3).[1,5]

1. Berbis P. Acitretin. *Ann Dermatol Venereol* 2001; 128: 737–45.
2. Lebwohl M, *et al.* Consensus conference: acitretin in combination with UVB or PUVA in the treatment of psoriasis. *J Am Acad Dermatol* 2001; 45: 544–53.
3. Lee CS, Koo J. A review of acitretin, a systemic retinoid for the treatment of psoriasis. *Expert Opin Pharmacother* 2005; 6: 1725–34.
4. British Association of Dermatologists. Psoriasis – general management. Available at: http://www.bad.org.uk/site/769/Default.aspx (accessed 25/05/10)
5. Ormerod AD, *et al.* BAD Clinical Standards Unit. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. *Br J Dermatol* 2010; 162: 952–63. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Acitretin%20Guidelines%202010.pdf (accessed 25/05/10)
6. Bruckner-Tuderman L, *et al.* Acitretin in the symptomatic therapy for severe recessive X-linked ichthyosis. *Arch Dermatol* 1988; 124: 529–32.
7. Steijlen PM, *et al.* Acitretin in the treatment of lamellar ichthyosis. *Br J Dermatol* 1994; 130: 211–14.
8. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; 154: 267–76.
9. van Dooren-Greebe RJ, *et al.* Acitretin monotherapy in Darier's disease. *Br J Dermatol* 1989; 121: 375–9.

Adverse Effects and Precautions

As for Isotretinoin, p. 1707.2 and p. 1709.2.

Acitretin has a relatively short half-life, but etretinate, which has a very prolonged half-life, has been detected in the plasma of some patients receiving acitretin. Recommendations vary slightly in different countries but pregnancy should be avoided for at least 2 to 3 years after treatment has been withdrawn (see also Pregnancy, below) and patients should not donate blood for at least 1 to 3 years after stopping therapy. Female patients should avoid alcohol during treatment with acitretin and for 2 months after stopping treatment (see under Interactions, below).

Breast feeding. Acitretin was distributed into the breast milk of a woman treated with oral acitretin for psoriasis. Although the estimated amount of acitretin that would be consumed by a breast-fed infant was only 1.5% of the maternal dose, the authors considered that the toxic potential of acitretin to the infant justified its avoidance. In this case, the infant was not breast-fed during acitretin therapy.[1] Licensed product information also recommends that breast-feeding women should not be given acitretin. The American Academy of Pediatrics, however, has found no mention of clinical effect on the infant, and considers the maternal use of acitretin to be usually compatible with breast feeding.[2]

1. Rollman O, Pihl-Lundin I. Acitretin excretion into human breast milk. *Acta Derm Venereol (Stockh)* 1990; 70: 487–90.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/09/07)

Capillary leak syndrome. There are rare reports of capillary leak syndrome associated with acitretin. In one case, generalised oedema and weight gain, haemorrhagic lesions, and evidence of rhabdomyolysis were seen.[1] In another, there was oedema and weight gain, dyspnoea, pulmonary infiltrates, pleural effusion, hypotension, and oliguria.[2] These reactions may be related to the retinoic acid syndrome that can occur with tretinoin (see p. 1726.2). Generalised oedema has also been reported with etretinate (p. 1704.1).

1. Estival JL, *et al.* Capillary leak syndrome induced by acitretin. *Br J Dermatol* 2004; 150: 150–2.
2. Vos LE, *et al.* Acitretin induces capillary leak syndrome in a patient with pustular psoriasis. *J Am Acad Dermatol* 2007; 56: 339–42.

Effects on the blood. For reports of adverse effects on the blood by oral retinoids, including agranulocytosis associated with acitretin, see under Isotretinoin, p. 1707.3.

Effects on the eyes. For reference to maculopathy occurring during therapy with acitretin, and the ocular effects of benign intracranial hypertension caused by retinoids, see under Isotretinoin, p. 1707.3.

Effects on the musculoskeletal system. For reference to myopathy occurring during therapy with acitretin, and a discussion of hyperostosis and calcinosis that can occur with oral retinoid therapy, see under Isotretinoin, p. 1708.2.

Effects on the skin. For mention of the exacerbation of erythroderma by acitretin, see under Isotretinoin, p. 1709.1.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies acitretin as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. The risks of spontaneous abortion and malformations similar to those associated with isotretinoin (p. 1709.3) are high when acitretin or etretinate are given during pregnancy, particularly the first trimester.[1,2] Although the risks might be lower after stopping treatment, malformations have still been reported in infants and aborted fetuses conceived within 2 years of stopping acitretin[1,3] and up to 45 months after stopping etretinate.[1] In the UK licensed product information for acitretin recommends that pregnancy should be avoided during and for at least 2 years (3 years is recommended in the USA) after withdrawal of therapy because etretinate, which has a much longer half-life than acitretin, has been detected in the plasma of some patients given acitretin. It has been pointed out that plasma-etretinate concentrations are a poor indication of total body stores; a study[4] has indicated that there may be substantial concentrations of etretinate in the fatty tissues of women who have received acitretin.

For information on contraceptive choice in women taking oral retinoids, see under Isotretinoin, p. 1709.3.

1. Geiger J-M, *et al.* Teratogenic risk with etretinate and acitretin treatment. *Dermatology* 1994; 189: 109–16.
2. Barbero P, *et al.* Acitretin embryopathy: a case report. *Birth Defects Res A Clin Mol Teratol* 2004; 70: 831–3.
3. Maradit H, Geiger J-M. Potential risk of birth defects after acitretin discontinuation. *Dermatology* 1999; 198: 3–4.
4. Sturkenboom MCJM, *et al.* Inability to detect plasma etretinate and acitretin is a poor predictor of the absence of these teratogens in tissue after stopping acitretin treatment. *Br J Clin Pharmacol* 1994; 38: 229–35.

Interactions

As for Isotretinoin, p. 1710.1.

Etretinate has been detected in the plasma of some patients receiving acitretin and acitretin is also a metabolite of etretinate; therefore interactions associated with etretinate (see p. 1704.1) may also apply to acitretin. Taking acitretin with alcohol has been associated with etretinate formation.

For discussion of the potential interactions of retinoids with hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Alcohol. The consumption of alcohol has been associated with the formation of etretinate in patients taking acitretin.[1,2] One study[2] found a trend suggesting that a higher alcohol intake was associated with a higher risk of etretinate formation and higher etretinate concentrations. However, the presence of alcohol is not essential for this transformation to take place and etretinate has also been detected in a patient taking acitretin who did not drink alcohol.[3] Consequently, licensed product information warns that alcohol must not be consumed by female patients during acitretin therapy and for 2 months after stopping, to avoid the formation of etretinate and associated prolonged risks of teratogenicity (see Pregnancy, above).

1. Larsen FG, *et al.* Conversion of acitretin to etretinate in psoriatic patients is influenced by ethanol. *J Invest Dermatol* 1993; 100: 623–7.
2. Larsen FG, *et al.* Acitretin is converted to etretinate only during concomitant alcohol intake. *Br J Dermatol* 2000; 143: 1164–9.
3. Maier H, Höntigsmann H. Concentration of etretinate in plasma and subcutaneous fat after long-term acitretin. *Lancet* 1996; 348: 1107.

Pharmacokinetics

Acitretin is absorbed from the gastrointestinal tract and peak plasma concentrations occur 1 to 5 hours after oral doses. Bioavailability after a single dose is about 60 to 70%, but this can vary considerably; bioavailability may be increased by dosage with food. Acitretin is highly bound to plasma proteins. It is metabolised to 13-*cis*-acitretin. Etretinate (p. 1703.3) has also been detected in the plasma of some patients after doses of acitretin. The elimination half-life of acitretin is about 2 days but account should always be taken

of the fact that the half-life of etretinate is much longer, being about 120 days. Acitretin is excreted as metabolites in bile and urine, and is distributed into breast milk.

General references.

1. Larsen FG, *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; 23: 42–61.
2. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; 190 (suppl): 1–33.
3. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; 39 (suppl): S25–S33.

Renal impairment. The pharmacokinetics of acitretin are reported to be altered in patients with chronic renal failure but neither acitretin nor its 13-*cis* metabolite are removed by haemodialysis.[1]

1. Stuck AE, *et al.* Pharmacokinetics of acitretin and its 13-cis metabolite in patients on haemodialysis. *Br J Clin Pharmacol* 1989; 27: 301–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Neotigason; *Austral.*: Neotigason; *Austria*: Neotigason; *Belg.*: Neotigason; *Braz.*: Neotigason; *Canad.*: Soriatane; *Chile*: Neotigason; *China*: Fang Xi (方希); Neotigason (新体卡松); Cz.: Neotigason; *Denm.*: Neotigason; *Fin.*: Neotigason; *Fr.*: Soriatane; *Ger.*: Neotigason; *Gr.*: Neotigason; *Hong Kong*: Neotigason; *Hung.*: Neotigason; *India*: Aceret; Acetec; Acitrin; *Irl.*: Neotigason; *Israel*: Neotigason; *Ital.*: Neotigason; *Malaysia*: Neotigason; *Mex.*: Neotigason; *Neth.*: Keraderm; Neotigason; Regioderm; *Norw.*: Neotigason; *NZ*: Neotigason; Novatretin; *Philipp.*: Neotigason; *Pol.*: Neotigason; *Port.*: Neotigason; *Rus.*: Neotigason (Неотигазон); *S.Afr.*: Neotigason; *Singapore*: Neotigason; *Spain*: Neotigason; *Swed.*: Neotigason; *Switz.*: Acicutan; Neotigason; *Thai.*: Neotigason; *Turk.*: Neotigason; *UK*: Neotigason; *USA*: Soriatane; *Venez.*: Neotigason.

Pharmacopoeial Preparations
BP 2014: Acitretin Capsules;
USP 36: Acitretin Capsules.

Adapalene *(BAN, USAN, rINN)*

Adapaleeni; Adapalen; Adapalène; Adapaleno; Adapalenum; CD-271; Адапален.

6-[3-(1-Adamantyl)-4-methoxyphenyl]-2-naphthoic acid.

$C_{28}H_{28}O_3$=412.5

CAS — 106685-40-9.

ATC — D10AD03.

ATC Vet — QD10AD03.

UNII — 1L4806J2QF.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Adapalene). A white or almost white powder. Practically insoluble in water and in alcohol; sparingly soluble in tetrahydrofuran.

USP 36: (Adapalene). A white or almost white powder. Practically insoluble in water; sparingly soluble in alcohol; soluble in tetrahydrofuran. Store in airtight containers. Protect from light.

Uses and Administration

Adapalene is a naphthoic acid derivative and retinoid analogue with actions similar to those of tretinoin (p. 1725.2). Adapalene is used in topical treatment of mild to moderate acne (p. 1682.2) where comedones, papules, and pustules predominate.

Adapalene is usually applied once daily at night as a 0.1% solution, cream, or gel to skin that has been cleansed and dried; a 0.3% gel is also available. Some patients may require less frequent applications. Other topical preparations that may cause irritation should not be used concurrently. If treatment with topical antibacterials or benzoyl peroxide is required, these should be applied in the morning and adapalene applied at night. However, a formulation combining adapalene with benzoyl peroxide, allowing simultaneous application, is available in some countries.

There may be apparent exacerbations of the acne during early treatment and a consistent therapeutic response may not be evident for at least 8 weeks. However, if there is no response after 12 weeks, therapy should be reassessed.

For use in young children, see below.

References.

1. Brogden RN, Goa KL. Adapalene: a review of its pharmacological properties and clinical potential in the management of mild to moderate acne. *Drugs* 1997; 53: 511–19.
2. Waugh J, *et al.* Adapalene: a review of its use in the treatment of acne vulgaris. *Drugs* 2004; 64: 1465–78.
3. Pariser DM, *et al.* Adapalene Study Group. The efficacy and safety of adapalene gel 0.3% in the treatment of acne vulgaris: a randomized, multicenter, investigator-blinded, controlled comparison study versus adapalene gel 0.1% and vehicle. *Cutis* 2005; 76: 145–51.
4. Thiboutot D, *et al.* Adapalene Study Group. Adapalene gel 0.3% for the treatment of acne vulgaris: a multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol* 2006; 54: 242–50.
5. Thiboutot DM, *et al.* Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol* 2006; 142: 597–602.
6. Gollnick HP, *et al.* Adapalene–BPO Study Group. Adapalene–benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009; 161: 1180–9.

Administration in children. Although not licensed for young children in the UK the *BNFC* includes adapalene 0.1% cream and gel, applied thinly once daily at night, for neonatal and infantile acne.

Adverse Effects and Precautions

As for Tretinoin, p. 1726.1 and p. 1726.3.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies adapalene as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Anophthalmia and agenesis of the optic chiasma were found in a fetus after termination of pregnancy in a woman who had applied adapalene 0.1% topically from the month before pregnancy until 13 weeks of gestation.[1]

1. Autret E, *et al.* Anophthalmia and agenesis of optic chiasma associated with adapalene gel in early pregnancy. *Lancet* 1997; 350: 339.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acnidazil; Adapne; Differin; Doniq; KM Gel; Panalene; Sinac; *Austral.*: Differin; *Austria*: Differin; *Belg.*: Differin; *Braz.*: Adacne; Adapel; Dalap; Deriva; Differin; *Canad.*: Differin; *Chile*: Adamed; Adiamil; Daplen†; Differin; Flamir; Nyskin; Zudenina; *China*: Differin (达芙文); *Cz.*: Differine; *Denm.*: Redap; *Fin.*: Differin; *Fr.*: Differine; *Ger.*: Differin; *Gr.*: Adaferin; *Hong Kong*: Aclear; Differin; Tifforly; *Hung.*: Differin; *India*: Aclene; Adaferin; Adapen; Adaple; Adaret; Adiff; Adlene-AD; Alangel; Alene; Apgel; Deriva; Difra; *Indon.*: Evalen; *Irl.*: Differin; *Israel*: Adaferin; *Ital.*: Differin; *Malaysia*: Deriva; Differin; T3 ADA; *Mex.*: Adaferin; Leneda; Trablene†; *Neth.*: Differin; *Norw.*: Differin; *NZ*: Differin; *Philipp.*: Differin; Klenzit; *Pol.*: Differin; *Port.*: Differin; *Rus.*: Clenzit (Клензит); Differin (Дифферин); *S.Afr.*: Differin; *Singapore*: Differin; *Spain*: Differine; *Swed.*: Differin; *Switz.*: Differin; *Thai.*: Differin; *Turk.*: Differin; Palexil; *UK*: Differin; *USA*: Differin; *Venez.*: Differin.

Multi-ingredient Preparations. *Arg.*: Epiduo; Panalene Duo; *Austral.*: Epiduo; *Belg.*: Epiduo; *Braz.*: Adacne Clin; Epiduo; *Canad.*: Tactuo; *Denm.*: Epiduo; Tactuo†; *Fin.*: Epiduo; *Fr.*: Epiduo; *Ger.*: Epiduo; *Gr.*: Epiduo; *Hong Kong*: Epiduo; *India*: Acneris-AD; Adacin; Clindapene; Clinderm-A; Deriva-C; Deriva-CMS; Epilene C; Faceclin-A; Feiz; Labopene-C; *Ital.*: Epiduo; *Norw.*: Epiduo; *NZ*: Epiduo; *Philipp.*: Epiduo; *Pol.*: Epiduo; *Port.*: Epiduo; *Rus.*: Clenzit-C (Клензит-С); *Singapore*: Epiduo; *Spain*: Epiduo; Tactuoben; *Swed.*: Epiduo; *Switz.*: Epiduo; *Thai.*: Epiduo; *UK*: Epiduo; *USA*: Epiduo.

Pharmacopoeial Preparations
BP 2014: Adapalene Cream; Adapalene Gel.

Alcloxa *(USAN, rINN)*

ALCA; Alcloxum; Aluminium Chlorhydroxyallantoinate; Aluminum Chlorhydroxy Allantoinate; Clorohidroxialantoinato de aluminio; RC-173; Альклокса.

Chlorotetrahydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl)ureato]dialuminium.

$C_4H_9Al_2ClN_4O_7$=314.6

CAS — 7317-25-5.

UNII — 1888O9DQA2.

Profile

Aldoxa is an astringent and keratolytic related to allantoin (p. 1693.1). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Babysan Powder.

Multi-ingredient Preparations. *Hong Kong*: Pilelife†; *Malaysia*: Neo-Medrol; *Thai.*: Neo-Medrol; *UK*: Dermidex.

Aldioxa *(USAN, rINN)*

ALDA; Aldioxum; Aluminium Dihydroxyallantoinate; Aluminum Dihydroxy Allantoinate; Dihidroxialantoinato de aluminio; Dihydroxyaluminum Allantoinate; RC-172; Альдиокса.

Dihydroxy[(2-hydroxy-5-oxo-2-imidazolin-4-yl)ureato]aluminium.

$C_4H_7AlN_4O_5$=218.1

CAS — 5579-81-7.

UNII — 8T66I31YNK.

Pharmacopoeias. In *Jpn.*

Profile

Aldioxa is an astringent and keratolytic related to allantoin (p. 1693.1). It is present in multi-ingredient preparations intended for various skin and gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Culmisa (卡尔萨); Ou Di Jia (欧迪佳); Xi Jing (悉景).

Multi-ingredient Preparations. *Arg.*: ZeaSorb; *Austral.*: ZeaSorb†; *Canad.*: ZeaSorb; *China*: CP Bright (正大维他); JieAn (揳安); *Fr.*: ZeaSorb; *Gr.*: Rikospray Silicone; *Indon.*: ZeaSorb; *Irl.*: ZeaSorb; *Israel*: Aronal Forte; *Ital.*: Rikospray; *Mex.*: Dentsiblen†; *Philipp.*: ZeaSorb; *S.Afr.*: ZeaSorb†; *Singapore*: ZeaSorb; *Thai.*: ZeaSorb†; *UK*: Cetanorm; ZeaSorb.

Alefacept *(BAN, USAN, rINN)*

Aléfacept; Alefaceptum; BG-9273; BG-9712; LFA3TIP; Recombinant Human LFA-3/1gG$_1$ Fusion Protein; Алефацепт.

A dimer of 1-92 antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C_H2-C_H3 γ1-chain).

CAS — 222535-22-0.

ATC — L04AA15.

ATC Vet — QL04AA15.

UNII — ELK3V90G6C.

Uses and Administration

Alefacept is a recombinant human fusion protein that binds to CD2 on memory T-lymphocytes, preventing their activation and reducing their number. It is used in the management of moderate to severe chronic plaque psoriasis (p. 1688.1) and is given in a dose of 15 mg once weekly by intramuscular injection, for 12 weeks. A second 12-week course may be given if necessary, starting not less than 12 weeks after the completion of the first.

General references.

1. Ellis CN, Krueger GG. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. *N Engl J Med* 2001; 345: 248–55.
2. Krueger GG, *et al.* A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002; 47: 821–33.
3. Krueger GG, Ellis CN. Alefacept therapy produces remission for patients with chronic plaque psoriasis. *Br J Dermatol* 2003; 148: 784–8.
4. Lebwohl M, *et al.* An international, randomized, double-blind, placebo-controlled phase 3 trial of intramuscular alefacept in patients with chronic plaque psoriasis. *Arch Dermatol* 2003; 139: 719–27.
5. Korman NJ, Moul DK. Alefacept for the treatment of psoriasis: a review of the current literature and practical suggestions for everyday clinical use. *Semin Cutan Med Surg* 2005; 24: 10–18.
6. Ortonne JP, *et al.* An open-label study of alefacept plus ultraviolet B light as combination therapy for chronic plaque psoriasis. *J Eur Acad Dermatol Venereol* 2005; 19: 556–63.
7. Mease PJ, *et al.* Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006; 54: 1638–45.
8. Strober BE, Menon K. Alefacept for the treatment of psoriasis and other dermatologic diseases. *Dermatol Ther* 2007; 20: 270–6.
9. Landells I, *et al.* Efficacy outcomes in patients using alefacept in the AWARE study. *J Cutan Med Surg* 2009; 13 (suppl 3): S122–S130.
10. Dunn LK, Feldman SR. Alefacept treatment for chronic plaque psoriasis. *Skin Therapy Lett* 2010; 15: 1–3.

Adverse Effects and Precautions

Chills are common on intravenous dosage of alefacept. Other adverse effects are cough, dizziness, headache, injection site pain and inflammation, myalgia, nausea, pharyngitis, and pruritus. More serious adverse reactions are cardiovascular events (including coronary artery disorder and myocardial infarction), hypersensitivity reactions, lymphopenia, and serious infections requiring hospitalisation. Cases of hepatotoxicity including asymptomatic transaminase elevation, fatty infiltration of the liver, hepatitis, and acute liver failure have occurred. Like other drugs with immunosuppressant actions, alefacept may increase the risk of malignancies, particularly basal or squamous cell cancers of the skin. It should not be given to patients with a history of malignancy.

Alefacept should also not be given to patients with pre-existing serious infections, and should be stopped if these develop. Its use should be considered carefully in patients with chronic infections or a history of recurrent infection.

Alefacept induces a dose-dependent reduction in circulating CD4+ and CD8+ T-lymphocyte counts. It is

therefore also contra-indicated in patients with HIV infection as the reduction in CD4+ T-lymphocytes could accelerate disease progression or increase complications of HIV infection. CD4+ T-lymphocyte counts should be monitored before starting alefacept therapy and then every 2 weeks during the 12-week treatment period. Treatment should not be started in patients with a CD4+ T-lymphocyte count below normal. Doses should be withheld and weekly monitoring started if the counts fall below 250 cells/microlitre, and treatment stopped if the counts remain below this level for one month.

Therapy should be stopped immediately, and appropriate treatment given, in patients who have anaphylaxis or serious hypersensitivity; it should not be restarted.

References.
1. Goffe B, *et al.* An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. *Clin Ther* 2005; 27: 1912–21.

Pharmacokinetics

Alefacept has a bioavailability of about 63% after intramuscular injection. After an intravenous dose it has an elimination half-life of about 11 to 12 days.

References.
1. Vaishnaw AK, TenHoor CN. Pharmacokinetics, biologic activity, and tolerability of alefacept by intravenous and intramuscular administration. *J Pharmacokinet Pharmacodyn* 2002; 29: 415–26.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Amevive†; *Canad.*: Amevive†; *Israel*: Amevive; *Switz.*: Amevive†; *USA*: Amevive.

Allantoin *(BAN, USAN)*

Alantoin; Alantoína; Alantoinas; Allantoiini; Allantoïne; Allantoinum; Glioxildiureído; Glyoxyldiureide; 5-Ureidohidantoína; Кордианин; Аллантоин.

5-Ureidohydantoin; 5-Ureidoimidazolidine-2,4-dione; 2,5-Dioxoimidazolidin-4-ylurea.

$C_4H_6N_4O_3$=158.1

CAS — 97-59-6.

UNII — 344S277G0Z.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Allantoin). A white or almost white, crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.

USP 36: (Allantoin). A white crystalline powder. Slightly soluble in water; very slightly soluble in alcohol.

Profile

Allantoin is an astringent and keratolytic. It is present in multi-ingredient preparations intended for various skin disorders and is also used for its astringent properties in preparations for the treatment of haemorrhoids and other anorectal disorders.

Psoriasis. In the USA the FDA decided that allantoin should be removed from lotions indicated for psoriasis as it was considered to be ineffective.[1]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; 5: 62.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Masse: *Pol.*: Alantan.

Multi-ingredient Preparations. *Arg.*: Abanta; Adermicina A Post Solar; Afonisan; Atomoderma A-E; Bushi; Contractubex; Crema Para Paspaduras†; Cremsor N; Cutidermin Emulsion Humectante†; Dermaloe; Esmedent con Fluor; Euroderm-A; Factor AE; Integrum; Lactocrem Bebe; Lociherp Liposomas Vitaminado; Masivol; Medic; Mencogrin AP; Mencogrin; Mencogrin; Novofarma; Pastillas Lorbi†; Pastillas Medex; Sebosoap; *Austral.*: Alphosyl†; Blistex Medicated Lip Ointment†; FootSmart; Hemocane; Macro Natural Vitamin E Cream; Medi Creme; Medi Pulv; Paxyl; SoloSite; Triple Care Cream; *Austria*: Contractubex; Rheumex†; *Braz.*: Contractubex; Fisioativ; Lactrex; Vitaderme; *Canad.*: Blistex Medicated Lip Ointment†; Polysporin Lip Treatment; *Chile*: Adolex; Dermaglos; Diencil; Nenegloss†; Pancrit; Queratopil; Sanoderm; Ureadin 30; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; *China*: Contractubex (康瑞保); Zhongxin (中鑫); *Cz.*: Contractubex; Jox; Panlid†; *Fr.*: Calmobrul; Cicatryl; Erygine†; Hydracuivre; Ilast Care; Ilast Hydra; Ilast O'Clean; Ilast Post-Op; Seborheane†; Spirial; Urgo Cicatrices; *Ger.*: Contractubex; Hydro Cordes; Hylo-Vision HD Plus; Ilast Care; Lipo Cordes; *Gr.*: Contractubex; Pisaveril; *Hong Kong*: Alox†; Alphate†; Aselan†; Contractubex; Egoderm; Egopsoryl TA; Pyodontyl†; *Hung.*: Contractubex; *India*: Acnederma; Acneguard; Acnestal; Aloederm-B; Alorex; Alphosyl; Anaproct; Anomex; Clin-3; Clin-3; Clinagel; Contractubex; Diafoot; Dibi; Elure; Hexilak; Mint; New Eye Lotion†; Shield; *Indon.*: Atopiclair; Mederma; Verile; *Irl.*: Pedamed; *Israel*: Atopiclair; Comfrey Plus; Proctozorin-N; Rekasitin†; Xclair; *Ital.*: Angstrom Viso; Biolastic T5; Centella Complex; Cerosteril; Cue Soluzione Otologica; Ginoxil Ecoschiuma; Keraflex; Resvelife Sole; Resvelife; Sensigel; Sensiquell; Tial-Z; Xerial; *Malaysia*: Dermaheal DeAkni; Dermaheal Post Laser Cream; Egoderm; Egopsoryl TA; *Mex.*: Antaderm; Contractubex; Dealan; Glossderm; Hipoglos Cremoso; Hipoglos; Lactrex; Mederma; Sebryl Plus; Sebryl; Sebstopp; Unguento de la Madre; *NZ*: Egoderm; Egopsoryl TA; Medipulv; *Philipp.*: Contractubex; Dermablend Colloidal Oatmeal Lotion; Hiruscar; *Pol.*: Alantan-Plus; Alantavit; Baikaderm; Cepan; Contractubex; Dernilan; Mucosit; Pupilek†; Septalan†; Tointex†; *Rus.*: Contractubex (Контрактубекс); Hepatrombin (Гепатромбин); Jox (Йокс); *S.Afr.*: Alphosyl†; Arola Rosebalm†; Blistex; Clearasil Medicated Facial Cleanser†; *Singapore*: Atopiclair; Egoderm; Egopsoryl TA; Erase; Hiruscar; Nu-Derm Toner; Octenisan; Purifying Gel; *Spain*: Alphosyl†; Antigrietun; Hepro: Polaramine Crema; *Switz.*: Alphastria; Baume Dalet; Contractubex; Gorgonium; Keli-med; Lyman; Optrex compresses†; PC 30 V; Sportium; *Thai.*: Opplin; *Turk.*: Contractubex; *UK*: Actinac†; Alphosyl HC†; Anodesyn; Atopiclair; Vesagex Heelbalm; *Ukr.*: Contractubex (Контрактубекс); Hepathrombin (Гепатромбин); Jox (Йокс); *USA*: Alasulf; Anbesol Cold Sore Therapy; Atopiclair; Blistex Lip Balm; Blistex; Deltavac; DIT1-2; Dr Dermi-Heal; Ionax Astringent; Orabase Lip; Tanac Dual Core; Tanac; *Venez.*: Alantamida; Lactrex.

Aloe Vera

Aloë; Алоэ Вера; Алоэ Древовидное.

ATC Herb — HA06AB5002 (Aloe vera: *dry leaf juice*); *HD02WA5001* (Aloe vera: *leaf mucilage*).

UNII — KIZ4X2EHYX (Aloe vera); *ZY81ZB3H0X* (Aloe vera *leaf*); *575DY8C1ER* (Aloe vera *flower*).

Profile

Aloe vera gel is a mucilaginous preparation obtained from the leaves of *Aloe vera* (*A. barbadensis*). It does not include the sap of *Aloe vera*, which contains anthraquinones, and should not be confused with aloes (p. 1816.1).

Aloe vera gel is widely used in cosmetics and toiletries for a reported moisturising and revitalising action. Aloe vera oil, which is reported to be made by macerating aloe vera in soybean, almond or apricot oils, is also used in cosmetics and toiletries.

References.
1. WHO. Aloe Vera Gel. *WHO Monographs on Selected Medicinal Plants*, volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/6.html (accessed 27/05/10)

Aloe vera is widely used in cosmetics and toiletries for a reported moisturising and revitalising action. There are also claims for the beneficial and even curative properties of aloe vera gel in the treatment of conditions such as acne, psoriasis, burns, wounds, arthritis, diabetes, hyperlipidaemia, peptic ulcer, and genital herpes.[1,2] Evidence to support these claims is lacking. There is also no strong evidence to support the use of aloe vera gel in the prevention or treatment of radiation-induced skin reactions in cancer patients.[3]

1. Marshall JM. Aloe vera gel: what is the evidence? *Pharm J* 1990; 244: 360–2.
2. Vogler BK, Ernst E. Aloe vera: a systematic review of its clinical effectiveness. *Br J Gen Pract* 1999; 49: 823–8.
3. Richardson J, *et al.* Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol)* 2005; 17: 478–84.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aloedent†; Amenite Vera; Barrocutina; Biorevit Gel; Puraloe Post Solar; Solenil Post Solar Cool Gel; *Braz.*: Aloax; Soapelle; *Fr.*: Veraskin†; *Ger.*: Pox-Clin†; Rinupret; *India*: Aloven; Jula; *Ital.*: Epitaloe; *Singapore*: Curacao.

Multi-ingredient Preparations. *Arg.*: Abanta; Acuaderm; Aftersun; Aloebel; Aristaloe; Aristaloe; Atomo Ordenador; Brunavera; Capson; Control Acne; Crema De Ordene; Cutidermin Crema Regeneradora†; Cutidermin Spray Humectante†; Dermaloe; Dermvien; Eurocolor Post Solar; Galenic Restaurador Capilar; KW; Maprosol Gel; Maternity Crema de Ordene; Mucobase; Negacne; Ocusun; Olamine; Omicohol A; Pervicol Toallas; Pervicol; Post Solar Nort; Puraloe Nutritiva; Puraloe; Recover Whitening; Refrane P; Refrane Plus; Repelente Zasu; Sadeltan F; Snella Vag; Solenil Post Solar; Talowin; Vera Plus; Xicanil Control NF Locion; Xyloprocto Toallas; *Austral.*: Aloe Vera Gel; Aloe Vera Plus; Lipz Ointment; Percutane†; Psor-Asist; Rapaid Rash-Relief; Triple Care Cream; Vicks Baby Balsam; *Austria*: Wick SinexAloe; *Braz.*: Actine; Actine; Malvatricin Natural Soft†; *Canad.*: Pure Gardens; *Chile*: Ac-Sal†; Acniben Toallitas; Cellenergy; Fray Romano; Glicoisdin; Micodual; Nenegloss†; Solarcaine Aloe Vera Gel; Ureadin Rx DB; Ureadin Rx RD; *Fr.*: Cicatridine; Rhinodoron; *Ger.*: Rhinodoron; *Hong Kong*: Pregnacare; *Hung.*: After Burn; *India*: Acnestal; Ale; Alo-E; Aloat NC; Alockin; Aloekin; Alogard; Alovit-AF; Alovit; Alv; Bioskin; Calosoft; Calvera; Cimfi; Coral; Dermamoist; Dew Derm; Dewsoft; Diabecon; Eelovit; Elovera-SPF; Elovera; Elovera; Evaren; Evecare; Evecare; Herr; Hidrate; Humidus; Ivan; Korisma; Moiste; Moisturex-AF; Nasoclear Aloegel; Sofderm; *Indon.*: Jointfit; Oramin-G; Velostin; *Israel*: Agisten with Aloe Vera; Aphtagone†; Aptha-X†; *Ital.*: Capso; Ekotrofil; Faringel; Ginoxil Ecoschiuma; Ninfagin; Proctocella Complex; Sclerovis H Plus; Vulnopur; *Malaysia*: A-Bruzzy; Elovera; Neo-Healar†; T3 Acne; TDF AHA Facial Wash for Oily/Acne Prone Skin; *Mex.*: Aloemagnolia; Gelconordin; Hipoglos Cremoso; *NZ*: Chap Stick; Lamisil Odor Eze†; Solarcaine Aloe; Vicks Baby Balsam; *Philipp.*: Elovera; Enfacare; Hiruscar; Intima†; Nap; *Port.*: Alkagin; *Rus.*: Elovera (Эловерa); *Singapore*: A-Bruzzy; Aze; Desitin Creamy; Hiruscar; *UK*: Antiac; Don't Bug Me; Sinose; *Ukr.*: Ambovit (Амбовит); Bon-Apetit (Бон-Аппетит); Eve Care (Ив Кер)†; Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: Aloe Grande; Biotene with Calcium; Bodi Kleen; Bodi Oil; Boudreaux's All Natural Butt Paste; Dermtex HC with Aloe; Duraflex Comfort; Entertainer's Secret; Geri-Lav Free; Gold Bond Medicated Triple Action Relief; Hawaiian Tropic Cool Aloe with I.C.E.; Hemorid For Women; Maximum Strength Flexall 454; Miaderm Radiation Relief; Mucotrol; Nasal-Ease; OraMagicRx; RadiaPlex Rx; Rx Support Heartburn & Acid Reflux Plus Aloe; Solarcaine Aloe Extra Burn Relief; Zim's Max Freeze; *Venez.*: Andantol Jalea; Fluciraс; Gameral; Gelsem; Jengimiel Sabila; Jengimiel.

Homoeopathic Preparations. *Canad.*: Hae 2 Complex†.

Aluminium Chloride

Aliuminio chloridas heksahidratas; Alumiinikloridiheksahydraatti; Aluminii Chloridum Hexahydricum; Aluminio, cloruro de; Aluminium Chloratum; Aluminium (chlorure d') hexahydraté; Aluminium-klorid-hexahidrát; Aluminiumkloridhexahydrat; Aluminum Chloride; Chlorid hlinitý hexahydrát; Cloreto de Alumínio; Cloruro de aluminio; Glinu chlorek; Алюминия Хлорид.

Aluminium chloride hexahydrate.

$AlCl_3.6H_2O$=241.4

CAS — 7446-70-0 (anhydrous aluminium chloride); 7784-13-6 (aluminium chloride hexahydrate).

ATC — D10AX01.

ATC Vet — QD10AX01.

UNII — LIF1N9568Y (aluminium chloride); 3CYT62D3GA (aluminium chloride hexahydrate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Aluminium Chloride Hexahydrate). A deliquescent, white or slightly yellow, crystalline powder or colourless crystals. Very soluble in water; freely soluble in alcohol; soluble in glycerol. Store in airtight containers.

USP 36: (Aluminum Chloride). Deliquescent, white or yellowish-white, practically odourless, crystalline powder. Its solutions are acid to litmus. Soluble 1 in 0.9 of water and 1 in 4 alcohol; soluble in glycerol. Store in airtight containers.

Uses and Administration

Aluminium chloride has astringent properties and is used in a 20% alcoholic solution as an antiperspirant in the treatment of hyperhidrosis (p. 1685.1). It is applied to dry skin, usually at bedtime, and is washed off in the morning before the sweat glands are fully active. Initially, it may be applied each night until sweating improves, then less frequently, as required, to maintain efficacy.

Homoeopathy

Aluminium chloride has been used in homoeopathic medicines under the following names: Aluminium muriaticum; Alumin mur.

References.
1. Scholes KT, *et al.* Axillary hyperhidrosis treated with alcoholic solution of aluminium chloride hexahydrate. *BMJ* 1978; 2: 84–5.
2. Ellis H, Scurr JH. Axillary hyperhidrosis - topical treatment with aluminium chloride hexahydrate. *Postgrad Med J* 1979; 55: 868–9.

Adverse Effects

Aluminium chloride may cause irritation especially if applied to damp skin; this is attributed to the formation of hydrochloric acid.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alumpak; Drysol; *Austral.*: Driclor; *Canad.*: Hemodent†; *Chile*: Drysol; Xerac AC; *Fr.*: Driclor; Etiaxil; *Ger.*: Gargarisma zum Gurgeln; Mallebrin Konzentrat; *Hong Kong*: Driclor; *Irl.*: Anhydrol Forte; Driclor†; *Israel*: Anhydrol Forte; *Malaysia*: Driclor†; *Mex.*: Drysol; *NZ*: Hidrosol†; *Philipp.*: Driclor; *Pol.*: Antidral; *S.Afr.*: Driclor; *Singapore*: Driclor; *Switz.*: Etiaxil; Racestyptine†; *UK*: Anhydrol Forte; Driclor; Odaban; *USA*: Drysol; Lumicain; Xerac AC.

Multi-ingredient Preparations. *Arg.*: Carnot Topico; *Canad.*: Racestyptine; *Chile*: Hidrofugal Forte†; Hidrofugal†; *Fr.*: Ephydrol; *Mex.*: Prespir; *Switz.*: Baume Dalet; *USA*: Stypto-Caine.

Pharmacopoeial Preparations

BP 2014: Aluminium Chloride Solution.

Aluminium Chlorohydrate

Aluminio, clorohidróxido de; Aluminium Chlorhydrate; Aluminium Chloride Hydroxide Hydrate; Aluminium Chlorhydroxide Aluminium Chloride Hydroxide Hydrate; Aluminum Chlorohydrate (USAN); Aluminum Hydroxychloride; Alüminyum Hidroksiklorür; Basic Aluminium Chloride; Clorohidrato de aluminio; Алюминия Хлоргидрат.

$Al_2(OH)_5Cl.xH_2O$

CAS — 1327-41-9 (anhydrous aluminium chlorohydrate).

ATC — D09AA08; M05BX02.

ATC Vet — QD09AA08; QM05BX02.

UNII — HPN8MZWT3M.

Pharmacopoeias. In *US*.

US also includes a range of compounds based on aluminium chlorohydrate. These are:

- aluminium dichlorohydrate and sesquichlorohydrate
- the polyethylene glycol (macrogol) complexes and propylene glycol complexes of aluminium chlorohydrex, aluminium dichlorohydrex, and aluminium sesquichlorohydrex
- the tri-, tetra-, penta-, and octachlorohydrates of aluminium zirconium and their respective glycine derivatives.

USP 36: (Aluminum Chlorohydrate). A 15% w/w solution in water has a pH of 3.0 to 5.0

Profile

Aluminium chlorohydrate is used similarly to aluminium chloride in hyperhidrosis (p. 1685.1). Single-ingredient products for hyperhidrosis generally have a concentration in the range of 10 to 25%.

Aluminium chlorohydrate is also included in a variety of dermatological preparations for its astringent and antiperspirant properties.

Aluminium toxicity. Bone pain, extreme fatigue, and raised aluminium concentrations in a woman with normal renal function were attributed to the use of an antiperspirant cream containing aluminium chlorohydrate 20%. She had been applying about 1 g of cream to each underarm daily for 4 years. Within 8 months of stopping the antiperspirant, plasma-aluminium concentrations had returned to normal and symptoms had resolved.[1]

1. Guillard O, *et al.* Hyperaluminemia in a woman using an aluminum-containing antiperspirant for 4 years. *Am J Med* 2004; 117: 956–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Bromhistop; Normoskin; Perspi; Sodorant; *Austral.*: QV Naked Anti-Perspirant Deodorant; *Canad.*: Avon Antiperspirant Deodorant†; Avon On Duty†; Creme Deodorant Multi-Soin Anti-Perspirant†; Hydrosal; Scholl Dry Antiperspirant Foot Aerosol Powder†; *Chile*: Hansaplast Footcare†; Hidrofugal†; *Fr.*: pM†; Spirial; *Ger.*: Phosphonorm; *India*: Aldry; *Israel*: Aloxan Derma†; *Ital.*: Spirial; *Mex.*: Skin Dry; *NZ*: Neat Effect; Neat Feat; Neat One; Neat Touch; *Port.*: Dermagor Antitranspirante; Lambda; *Switz.*: Gelsica†; Phosphonorm; *Turk.*: Anti-Fosfat Al; Kursept; Terkur; *UK*: Chiron Barrier Cream; *USA*: Bromi-Lotion.

Multi-ingredient Preparations. *Arg.*: Neobitiol; Sodorant; *Austral.*: Neo-Medrol†; *Austria*: Sulgan 99; *Canad.*: Feet Athletes Foot and Antifungal†; Medrol Acne Lotion; Neo-Medrol Acne; *Chile*: Hidrofugal Forte†; Hidrofugal†; Normaderm Stick Secante Camufu Imperfecciones; Uriage Desodorante Tri-Actif; *Fr.*: Spirial; *Gr.*: Medrol Acne Lotion; Neo-Medrol; *Hong Kong*: Neo-Medrol Acne; *India*: Handid; *Indon.*: Betiga†; *Israel*: Fungimon; Neo-Medrol; Pedisol†; *S.Afr.*: Neo-Medrol†; *Singapore*: Neo-Medrol; *Spain*: Hongosan†; *Turk.*: Pers-Mant; *USA*: Breeze Mist Foot Powder; Ostiderm.

Pharmacopoeial Preparations

USP 36: Aluminum Chlorohydrate Solution; Aluminum Dichlorohydrate Solution; Aluminum Sesquichlorohydrate Solution; Aluminum Zirconium Octachlorohydrex Gly Solution; Aluminum Zirconium Pentachlorohydrate Solution; Aluminum Zirconium Pentachlorohydrex Gly Solution; Aluminum Zirconium Tetrachlorohydrate Solution; Aluminum Zirconium Tetrachlorohydrex Gly Solution; Aluminum Zirconium Trichlorohydrate Solution; Aluminum Zirconium Trichlorohydrex Gly Solution.

Amiloxate *(USAN, rINN)*

Amiloxatum; Amiloxatum; E-1000; Isoamyl *p*-Methoxycinnamate; Амилоксат.

Isopentyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 3-methylbutyl ester.

$C_{15}H_{20}O_3$=248.3

CAS — 71617-10-2.

UNII — 376KTP06KB.

NOTE. Neo-Heliopan E 1000 is a trade name that has been used for amiloxate.

Pharmacopoeias. In *US*.

USP 36: (Amiloxate). Store in airtight containers.

Profile

Amiloxate, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lelco.

Multi-ingredient Preparations. *Arg.*: Fotoprotector Extrem; Fotoprotector; Lelco Labial; Lelco P Ultra; Lelco Spray; Lelco Ultrablock Extreme; Lelco Ultrablock†; Ozonosol; *Austral.*: Sunsense; *Braz.*: Fotoprotetor Spray Isdin†; *Chile*: Ansolar; Emolan Gel Protector Solar; Emolan†; Fotoprotector Isdin Extrem†; Fotoprotector Isdin-25 Pediatrics†; *Ger.*: Daylong actinica†; *Hong Kong*: Sunsense†; *Malaysia*: Sunsense Sport Gel†; Sunsense Sport†; *Singapore*: Sunsense Sport†; *Switz.*: Daylong actinica; *UK*: Uvistat.

Aminobenzoic Acid

Acide 4-Aminobenzoïque; Acidum 4-Aminobenzoicum; Amben; 4-Aminobensoesyra; 4-Aminobentsoehappo; 4-aminobenzoesav; Aminobenzoico, ácido; 4-Aminobenzoinė rūgštis; Kwas 4-aminobenzoesowy; Kyselina 4-aminobenzoová; PAB; PABA; Pabacidum; Para-aminobenzoic Acid; Vitamin Bx; Vitamin H'; Аминобензойная Кислота.

4-Aminobenzoic acid.

$C_7H_7NO_2$=137.1

CAS — 150-13-0.

ATC — D02BA01.

ATC Vet — QD02BA01.

UNII — TL2TJE8QTX.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (4-Aminobenzoic Acid; Aminobenzoic Acid BP 2014). White or slightly yellow crystalline powder. Slightly soluble in water; freely soluble in alcohol; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Aminobenzoic Acid). White or slightly yellow, odourless crystals or crystalline powder. It discolours on exposure to air or light. Slightly soluble in water and in chloroform; freely soluble in alcohol and in solutions of alkali hydroxides or carbonates; sparingly soluble in ether. Store in airtight containers. Protect from light.

Uses and Administration

Aminobenzoic acid is applied topically as a sunscreen (p. 1681.3). Aminobenzoic acid and its derivatives effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Aminobenzoate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity.

Aminobenzoic acid has sometimes been included as a member of the vitamin-B group, but deficiency of aminobenzoic acid in man or *animals* has not been found.

Aminobenzoic acid has been used with bentiromide (p. 2454.3) in the PABA or BTPABA test of pancreatic function.

Adverse Effects and Precautions

Adverse skin reactions such as local irritation and contact dermatitis have been reported after the topical use of aminobenzoate sunscreens. Aminobenzoate sunscreens should not be used by those with a history of photosensitivity or hypersensitivity reactions to structurally related drugs such as sulfonamides, thiazide diuretics, and ester-type local anaesthetics.

Aminobenzoic acid may stain clothing.

Allergic and photoallergic contact dermatitis have been reported after topical use of aminobenzoic acid or its esters.[1] Early reports of such reactions led to the removal of these compounds from sunscreen preparations (many are now described as 'PABA-free'), although padimate O still appears to be widely used.[2] Patients allergic to aminobenzoic acid may also react to structurally related allergens such as para-aminobenzoic acid ester anaesthetics, sulfonamides, and paraphenylenediamine in hair dyes.[1,2]

Skin reactions (vitiligo) have also been reported with oral aminobenzoic acid[3] and the adverse effects associated with the former use of high oral doses for various conditions have been highlighted.[4]

1. Scheuer E, Warshaw E. Sunscreen allergy: A review of epidemiology, clinical characteristics, and responsible allergens. *Dermatitis* 2006; 17: 3–11. Correction. *ibid.*; 162.
2. Mackie BS, Mackie LE. The PABA story. *Australas J Dermatol* 1999; 40: 51–3.
3. Hughes CG. Oral PABA and vitiligo. *J Am Acad Dermatol* 1983; 9: 770.
4. Worobec S, LaChine A. Dangers of orally administered para-aminobenzoic acid. *JAMA* 1984; 251: 2348.

Pharmacokinetics

If given orally, aminobenzoic acid is absorbed from the gastrointestinal tract. It is metabolised in the liver and excreted in the urine as unchanged drug and metabolites.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Pabasun; Paraminan; *India*: Pabalak; Pabatab; Paraminol; *Rus.*: Actipol (Актипол); *Spain*: Hachemina Fuerte†; *Ukr.*: Actipol (Актипол).

Multi-ingredient Preparations. *Arg.*: Biorevit Solar 15; *Braz.*: Pantogar; *Cz.*: Revalid; *Hong Kong*: Pantogar; *Hung.*: Revalid; *India*: Melanocyl; Melonil; Menofit; Menopace Iso; Menopace; Pabatab-BZ; *Indon.*: Pantogar; *Mex.*: Pabafilm†; Pantogar; *Rus.*: Pantovigar (Пантовигар); *Singapore*: Pantogar; *Spain*: Tri Hachemina†; *Switz.*: Pantogar; Revalid†; *Turk.*: Pantogar; *Ukr.*: Pantogar (Пантогар); Vitrum Beauty (Витрум Бьюти); Vitrum Beauty Elite (Витрум Бьюти Элит); *USA*: PowerVites.

Pharmacopoeial Preparations

USP 36: Aminobenzoic Acid Gel; Aminobenzoic Acid Topical Solution.

Ammonium Lactate *(USAN)*

Amonio, lactato de; BMS-186091; Аммония Лактат.

$C_3H_9NO_3$=107.1

CAS — 52003-58-4.

ATC Vet — QA16QA04.

UNII — 67M901L9NQ.

Profile

Ammonium lactate is a humectant applied as a cream or lotion containing 12% lactic acid neutralised with ammonium hydroxide. It is used in the treatment of dry scaly conditions of the skin including ichthyosis. Adverse effects of topical ammonium lactate preparations include transient erythema, burning, and stinging. Treated areas may be more sensitive to sunlight and exposure should be minimised.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lacto-Cev; Lactrex; Nutrafilm; *Braz.*: Lac-Hydrin†; *Fr.*: Kerapil; *India*: Lak-Am-Lact; *Malaysia*: Lanate; *Mex.*: Lac-Hydrin; *NZ*: Lac-Hydrin†; Lanate†; *Singapore*: Lanate; *USA*: al12; Amlactin; Geri-Hydrolac; Halonate; Kerasal AL; Lac-Hydrin; LAC-Lotion.

Multi-ingredient Preparations. *Arg.*: Clobeplus; Clobesol LA; Dermexane; Lactiderm; Lacto-Cev Zn; *Braz.*: Lactrex; *Chile*: Queratopil; *Fr.*: I-Soft; Zeniac LP Fort; Zeniac LP; Zeniac; *Indon.*: Exfoliac†; *Ital.*: Alfa Acid; Ipso Urea; *Mex.*: Lactrex; *USA*: Carb-O-Lac HP; Halac Kit; Kerasal Ultra; Ultralytic 2; *Venez.*: Lactrex.

Arbutin

Arbutoside; Arbutyna; Beta-arbutin; Ursin; Арбутин.

4-Hydroxyphenyl-β-D-glucopyranoside.

$C_{12}H_{16}O_7$=272.3

CAS — 497-76-7 (beta-arbutin); 84380-01-8 (alpha-arbutin).

UNII — C5INA23HXF.

Profile

Arbutin is a glycosylated derivative of hydroquinone (p. 1705.1) extracted from bearberry (p. 2453.2) and similar plants. It is used topically in concentrations of 1 to 5% as a depigmenting agent for the skin in hyperpigmentation disorders. The higher concentrations may lead to a paradoxical hyperpigmentation.

Alpha-arbutin has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cellskinlab Phyto Spot; Meiasoft; *Chile*: Phyto Corrective Gel†; Phyto Spot; Recover Ol; *Fr.*: Effasun Depigmentante; *India*: Carofit; Demelan; Kojivit; Niltan; *Ital.*: Brunex; *Port.*: Despigmentante†.

Avobenzone *(USAN, rINN)*

Avobenzona; Avobenzonum; Butylmethoxydibenzoylmethane; 4-*tert*-Butyl-4'-methoxydibenzoylmethane; Авобензон.

1-(*p*-*tert*-Butylphenyl)-3-(*p*-methoxyphenyl)-1,3-propanedione; 1-[4-(1,1-dimethylethyl)phenyl]-3-(4-methoxyphenyl)-1,3-propanedione.

$C_{20}H_{22}O_3$=310.4

CAS — 70356-09-1.

UNII — G63QQF2NOX.

NOTE. Escalol 517, Eusolex 9020, Neo-Heliopan 357, and Parsol 1789 are trade names that have been used for avobenzone.

Pharmacopoeias. In *US*.

USP 36: (Avobenzone). Store in airtight containers. Protect from light.

Profile

Avobenzone is a substituted dibenzoylmethane used by topical application as a sunscreen (p. 1681.3). Dibenzoylmethanes absorb light in the UVA range (for definitions, see p. 1685.3) and may therefore be used with other sunscreens that absorb UVB light to prevent sunburn; they will also provide some protection against drug-related or other photosensitivity reactions associated with UVA light.

Contact and photocontact allergic dermatitis has occasionally been reported with the topical use of dibenzoylmethane sunscreens.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Lelco; ***Canad.***: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; Silkies Enriche; ***Chile***: ROC Minesol Bronze.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Avotermin *(rINN)*

Avotermina; Avotermine; Avoterminum; Human Recombinant Transforming Growth Factor β3; TGF-β3; Авотермин.

CAS — 182212-66-4.

UNII — 2Q1G525JWN.

NOTE. The name Juvista has been used as a trade mark for avotermin.

Profile

Avotermin is a human recombinant transforming growth factor β3 under investigation to improve scar tissue appearance following surgery. It is given as an intradermal injection around the margins of the wound site.

References.

1. Bush J, *et al.* Therapies with emerging evidence of efficacy: avotermin for the improvement of scarring. *Dermatol Res Pract* 2010. Available at: http://www.hindawi.com/journals/drp/2010/690613.html (accessed 25/10/10)
2. Occleston NL, *et al.* Avotermin for the improvement of scar appearance: a new pharmaceutical in a new therapeutic area. *Expert Opin Invest Drugs* 2009; 18: 1231–9.
3. Ferguson MWJ, *et al.* Prophylactic administration of avotermin for improvement of skin scarring: three double-blind, placebo-controlled, phase I/II studies. *Lancet* 2009; 373: 1264–74.

Azelaic Acid *(USAN, rINN)*

Acide azélaïque; Ácido anchoico; Ácido azelaico; Ácido lepargílico; Acidum Azelaicum; Anchoic acid; Atseläiinihappo; Azelaico, ácido; Azelaik Asit; Azelainsyra; Lepargylic acid; ZK-62498; Азелаиновая Кислота.

Nonanedioic acid; Heptane-1,7-dicarboxylic acid.

$C_9H_{16}O_4$=188.2

CAS — 123-99-9.

ATC — D10AX03.

ATC Vet — QD10AX03.

UNII — F2VW3D43YT.

Uses and Administration

Azelaic acid inhibits the growth of *Propionibacterium* spp. and reduces keratinisation. It is used in the topical treatment of mild to moderate inflammatory acne (p. 1682.2) and for the inflammatory papules and pustules of mild to moderate rosacea (p. 1688.3). It has also been tried in hyperpigmentary skin disorders such as melasma, and in malignant melanoma.

In the treatment of **acne** azelaic acid is applied twice daily for up to 6 months as a 20% cream or 15% gel. Improvement usually occurs within four weeks.

For the treatment of mild to moderate **rosacea**, a 15% gel should be applied to the affected area twice daily. Improvement usually occurs in 4 to 8 weeks; optimum results are usually seen after several months of treatment.

References.

1. Pitton A, Goa KL. Azelaic acid: a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. *Drugs* 1991; 41: 780–98.
2. Breathnach AS. Melanin hyperpigmentation of skin: melasma, topical treatment with azelaic acid, and other therapies. *Cutis* 1996; 57 (suppl): 36–45.
3. Elewski B, Thiboutot D. A clinical overview of azelaic acid. *Cutis* 2006; 77 (suppl): 12–16.
4. Del Rosso JQ. The use of topical azelaic acid for common skin disorders other than inflammatory rosacea. *Cutis* 2006; 77 (suppl): 22–4.
5. Liu RH, *et al.* Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. *Arch Dermatol* 2006; 142: 1047–52.

Adverse Effects and Precautions

Topical application of azelaic acid may produce a transient skin irritation such as burning, stinging, pruritus, dryness, and scaling. It is usually mild and disappears on continued treatment, but in a few patients the irritation may persist, requiring reduced frequency of application or temporary suspension of treatment. There have been rare reports of hypopigmentation, rash, and photosensitivity. Azelaic acid should not be applied to the eyes, mouth, or other mucous membranes.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies azelaic acid as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cutacelan; ***Austral.***: Azclear; Finacea; Skinoren†; ***Austria***: Skinoren; ***Belg.***: Skinoren; ***Braz.***: Azelan; Dermazelaic; Dermizan; ***Canad.***: Finacea; ***Cz.***: Aknoren; Skinoren; ***Denm.***: Finacea; Skinoren; ***Fin.***: Skinoren; ***Fr.***: Finacea; Skinoren; ***Ger.***: Skinoren; ***Gr.***: Alenzantyl; Arbonid; Azedose; Azelac; Azelaxine; Azelderm; Cevigen; Chemilaic; Exazen; Forcilen; Kenedril; Noreskin; Opilet; Prevolac; Skinoren; Sonalent; Zelicrema; Zorkenil; Zumilin; ***Hong Kong***: Qualicren; Qualilaic; Skinoren; ***Hung.***: Finacea; Skinoren; ***India***: Aziderm; ***Indon.***: Aza 20; Skinoren†; Zelface; Zeliris; ***Irl.***: Skinoren; ***Israel***: Skinoderm; ***Ital.***: Finacea; Neocutis; Skinoren; ***Malaysia***: Acnederm Lotion; Skinoren; ***Mex.***: Finacea; ***Neth.***: Finacea; ***Norw.***: Finacea; Skinoren; ***NZ***: Skinoren; ***Philipp.***: Skinoren†; ***Pol.***: Acne-Derm; Finacea; Hascoderm; Skinoren; ***Port.***: Dermazil†; Finacea; Skinoren; ***Rus.***: Skinoren (Скинорен); ***S.Afr.***: Skinoren; ***Singapore***: Skinoren; ***Spain***: Finacea; Skinoren; Zelaika†; Zeliderm; ***Swed.***: Finacea; Skinoren; ***Switz.***: Skinoren; ***Thai.***: Skinoren; ***Turk.***: Azelderm; Finacea; Skinoren; ***UK***: Finacea; Skinoren; ***Ukr.***: Acnestop (Акнестоп); Azogel (Азогель); Skinoren (Скинорен); ***USA***: Azelex; Finacea; Finevin; ***Venez.***: Cutacelan.

Multi-ingredient Preparations. ***Fr.***: Melascreen Depigmentant; ***Hong Kong***: Acnederm; ***Ital.***: Zeroac; ***NZ***: Acnederm; ***Singapore***: Acnederm; Bio-Tachest†; ***USA***: NicAzel Forte; Tri-zel; VP-Zel.

Becaplermin *(BAN, USAN, rINN)* ⊗

Becaplermina; Bécaplermine; Becalplerminum; Bekaplermiini; Bekaplermin; RWJ-60235; Бекаплермин.

Recombinant human platelet-derived growth factor BB.

CAS — 165101-51-9.

ATC — A01AD08; D03AX06.

ATC Vet — QA01AD08; QD03AX06.

UNII — 1B56C968OA.

Uses and Administration

Becaplermin is a recombinant human platelet-derived growth factor (rhPDGF-BB) that enhances the formation of granulation tissue and promotes wound healing (p. 1690.1).

Becaplermin is used in the management of full thickness neuropathic diabetic skin ulcers (see Diabetic Foot Disease, p. 464.2). It is applied topically as a 0.01% gel once daily, covered by a moist saline gauze dressing. If no meaningful healing process (decrease in ulcer size of about 30%) is evident after 10 weeks of therapy, or complete healing has not occurred in 20 weeks, treatment should be re-assessed.

Becaplermin is used with a resorbable synthetic calcium phosphate matrix in products which promote bone and tissue growth in the treatment of periodontal disease or in orthopaedic surgery for foot and ankle fusion. They are also under investigation in the treatment of osteonecrosis of the jaw, fractures, and osteoporosis, and in the repair of cartilage, ligament, and tendon injuries.

References.

1. Nagai MK, Embil JM. Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. *Expert Opin Biol Ther* 2002; 2: 211–18.
2. Nevins M, *et al.* Platelet-derived growth factor stimulates bone fill and rate of attachment level gain: results of a large multicenter randomized controlled trial. *J Periodontol* 2005; 76: 2205–15.
3. McGuire MK, *et al.* rhPDGF-BB promotes healing of periodontal defects: 24-month clinical and radiographic observations. *Int J Periodontics Restorative Dent* 2006; 26: 223–31. Correction. *ibid.* 2007; 27: 88.
4. Fang RC, Gallano RD. A review of becaplermin gel in the treatment of diabetic neuropathic foot ulcers. *Biologics* 2008; 2: 1–12.
5. Graham S, *et al.* Investigating the role of PDGF as a potential drug therapy in bone formation and fracture healing. *Expert Opin Invest Drugs* 2009; 18: 1633–54.
6. Papanas N, Maltezos E. Benefit-risk assessment of becaplermin in the treatment of diabetic foot ulcers. *Drug Safety* 2010; 33: 455–61.

Adverse Effects and Precautions

Becaplermin is contra-indicated if there is active infection at the application site, because adverse effects such as cellulitis, osteomyelitis, and deep wound infections have been reported, depending on the product used. If the site becomes infected during therapy, treatment should be stopped until the infection clears, or, if surgically used, consideration should be given to removing the grafting material containing becaplermin. Other adverse effects include application site reactions such as pain, erythema, or swelling.

The surgical use of becaplermin may also cause anaphylaxis, bleeding, haematoma, wound dehiscence, and local or peripheral neuralgia; caution is advised in patients with severe endocrine-induced diseases, or those receiving immunosuppressive therapy or conditions that may cause bleeding complications. When used orthopaedically, becaplermin should not be implanted in patients with metabolic disorders known to adversely affect the skeleton, such as renal osteodystrophy or hypercalcaemia.

Becaplermin should not be used if the patient has neoplasms at or near the site of topical application or periodontal use. Furthermore, some manufacturers have contra-indicated it in any known malignancy.

Carcinogenicity. Malignancies distant from the application site of topical becaplermin have been seen in a clinical study and in postmarketing use, according to licensed product information. Also, a review conducted by the EMEA, which included an epidemiological study, showed an increase in death rate from all cancers in patients treated with 3 or more tubes of becaplermin gel [tube size unspecified].[1] However, this review concluded that the overall risk of developing cancer was not significantly different between users and non-users. Based on these findings and acknowledging the study's limitations, the EMEA[1] and MHRA[2] have nonetheless recommended that becaplermin should not be used in patients with any form of cancer.

1. EMEA. Questions and answers on the review of Regranex (becaplermin). Outcome of a procedure under Article 20 of Regulation (EC) No 726/2004 (issued 18th February 2010). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2010/02/WC500074138.pdf (accessed 16/11/10)
2. MHRA/CHM. Becaplermin (Regranex) for diabetic ulcers: contra-indicated in patients with any known current cancer. *Drug Safety Update* 2010; 3 (9): 10. Available at: http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON076501 (accessed 01/11/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austria***: Regranex†; ***Canad.***: Regranex†; ***Cz.***: Regranex†; ***Fr.***: Regranex†; ***Ger.***: Regranex†; ***Gr.***: Regranex; ***Irl.***: Regranex†; ***Israel***: Regranex†; ***Mex.***: Regranex; ***Neth.***: Regranex†; ***Port.***: Regranex†; ***Spain***: Regranex†; ***Switz.***: Regranex†; ***UK***: Regranex†; ***USA***: Regranex.

Multi-ingredient Preparations. ***Canad.***: Augment Bone Graft; ***USA***: GEM 21S.

Bemotrizinol *(USAN, rINN)*

Bemotrizinol; Bemotrizinolum; BEMT; Bis-ethylhexyloxyphenol Methoxyphenol Triazine; FAT-70884; Бемотризинол.

2,2'-[6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl]bis[5-[(2-ethylhexyl)oxy]phenol].

$C_{38}H_{49}N_3O_5$=627.8

CAS — 187393-00-6.

UNII — PWZ1720C8H.

NOTE. Tinosorb S is a trade name that has been used for bemotrizinol.

Profile

Bemotrizinol is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Eucerin; *Fr.*: Daylong Ultra; *Singapore*: Sunsense Anti-Ageing.

Multi-ingredient Preparations. *Arg.*: Cetaphil UV Defense; Eucerin Sun Protection 3D; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Pediatrics†; Fotoprotector Ultra; Polysianes; Protector Labial Extrem; *Austral.*: Hamilton Family Sunscreen; Hamilton Toddler; Sunsense Anti Ageing Face; Sunsense Bronze Shield; Sunsense Lip Balm†; Sunsense Moisturising Face; *Braz.*: Sundown Kids Colour; Sundown Kids Colour; Sundown Kids; Sundown Mousse; Sundown Spray; Sundown; Sundown; *Canad.*: Anthelios; ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; *Chile*: Ansolar; Avene Spray 50+; Eucerin Hydro-Protect; Eucerin Ninos; Eucerin Solar†; Eucerin; Eucerin; Eucerin; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Hyaluron; Nutraisdin; Photoscreen†; Protector Labial Extrem†; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; *Fr.*: Anthelios; Anthelios; Daylong; Melascreen solaire; Sun LEB; *Ger.*: Daylong actinica†; *Hong Kong*: Sun-Sense Anti-ageing Face Matte; *Malaysia*: Cetaphil UVA/UVB Defense; SunSense Anti-Ageing Face; *Mex.*: Eclipsol Clarity; Eclipsol Forte; Eclipsol Hydro; Eclipsol Ultra; ProZone Baby; ProZone Ultra Fluido; *NZ*: Hamilton Toddler; *Singapore*: Cetaphil UVA/UVB; Lipoderm; Sunsense Moisturising Face; *Switz.*: Daylong actinica; *Thai.*: Eucerin Sun Sensitive Skin†; Sebamed Multi Protect Suncream; *UK*: Anthelios XL; Spotner; Uvistat Lipscreen.

Bentoquatam *(USAN)*

Quaternium 18-bentonite; Quaternium-18 bentonita; Бентоквагам.

Bis(hydrogenated tallow alkyl)dimethylammonium complex with sodium bentonite.

CAS — 1340-69-8.

Profile

Bentoquatam, described as an organoclay compound, is a barrier preparation that is applied topically as a 5% lotion to prevent allergic contact dermatitis caused by poison ivy, poison oak, or poison sumac. The lotion is applied in a sufficient quantity to form a visible coating 15 minutes before possible contact with the plants. If continued protection is required the lotion may be re-applied every 4 hours or at any time if the visible coating is removed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Ivy Block.

Benzoyl Peroxide *(USAN)*

Bensoylperoxid; Bentsoyyliperoksidi; Benzoilo peroksidas; Benzoil-peroxid; Benzoyil Peroksit; Benzoylis Peroxidum; Benzoylperoxid; NSC-675; Peróxido de benzoílo; Peroxyde de benzoyle; Пероксид бензоила; Бензоил пероксид.

Dibenzoyl peroxide.

$C_{14}H_{10}O_4$=242.2

CAS — 94-36-0 (anhydrous benzoyl peroxide).

ATC — D10AE01.

ATC Vet — QD10AE01; QD11AX90.

UNII — W9WZN9A0GM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Benzoyl Peroxide, Hydrous). It contains not less than 70% and not more than 77% of anhydrous benzoyl peroxide and not less than 20% of water. It rapidly loses water on exposure to air and may explode if the water content is too low. A white or almost white, amorphous or granular powder. Practically insoluble in water; slightly soluble in alcohol; soluble in acetone; soluble in dichloromethane with separation of water. Store at 2 degrees to 8 degrees in a container that has been treated to reduce static charges and that has a device for the release of excess pressure. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine after acidification with dilute hydrochloric acid. Protect from light.

USP 36: (Hydrous Benzoyl Peroxide). It contains a minimum of 20% of water for the purpose of reducing flammability and shock sensitivity. The hydrous form is a white granular powder with a characteristic odour. Sparingly soluble in water and in alcohol; soluble in acetone, in chloroform, and in ether. Store in the original container, treated to reduce static charges. Unused material should not be returned to its original container but should be destroyed by the addition of sodium hydroxide solution (10%). Destruction can be considered to be complete if the addition of a crystal of potassium iodide does not result in the release of free iodine.

Uses and Administration

Benzoyl peroxide has mild keratolytic properties. Its antimicrobial action is probably due to its oxidising effect and activity has been reported against *Staphylococcus epidermidis* and *Propionibacterium acnes*. It is used mainly in the treatment of acne (below), applied once or twice daily in topical preparations usually containing 2.5 to 10%, sometimes with other antimicrobials. For use in young children, see below. It has been used similarly in the treatment of fungal skin infections (p. 568.1), such as tinea pedis although other drugs are usually preferred. A 20% lotion has been applied every 8 to 12 hours in the treatment of decubitus or stasis ulcers. Strengths are expressed as anhydrous benzoyl peroxide although it is used in a hydrous form for safety (see Pharmacopoeias, above).

Benzoyl peroxide is also used as a bleaching agent in the food industry and as a catalyst in the plastics industry.

Acne. Benzoyl peroxide applied topically in concentrations of up to 10% is probably the most widely used first-line drug in the management of mild acne (p. 1682.2). Early studies in *animals* found benzoyl peroxide to be sebosuppressive[1] but later studies showed that sebum excretion rises during the first few months of treatment,[2,3] probably due to the comedolytic action of benzoyl peroxide, and remains at a stable level thereafter. Benzoyl peroxide has been shown to have a significant inhibitory effect on skin microflora, with reductions in surface and follicular microorganisms within 48 hours of beginning treatment, but clinical improvement took several more days to appear.[4] The combined use of benzoyl peroxide with topical clindamycin or erythromycin can inhibit the development of antibacterial resistance and bring about clinical improvement when resistance already exists.[5]

1. Gloor M, *et al.* Cytokinetic studies on the sebo-suppressive effect of drugs using the example of benzoyl peroxide. *Arch Dermatol Res* 1980; 267: 97–9.
2. Cunliffe WJ, *et al.* Topical benzoyl peroxide increases the sebum excretion rate in patients with acne. *Br J Dermatol* 1983; 109: 577–9.
3. Pierard-Franchimont C, *et al.* Topical benzoyl peroxide increases the sebum excretion rate. *Br J Dermatol* 1984; 110: 506.
4. Bojar RA, *et al.* The short-term treatment of acne vulgaris with benzoyl peroxide: effects on the surface and follicular cutaneous microflora. *Br J Dermatol* 1995; 132: 204–8.
5. Taylor GA, Shalita AR. Benzoyl peroxide-based combination therapies for acne vulgaris: a comparative review. *Am J Clin Dermatol* 2004; 5: 261–5.

Administration in children. In addition to its use in adolescents with acne, benzoyl peroxide has also been used topically in the treatment of neonatal and infantile acne; it may be applied once or twice daily starting with lower strength preparations of 2.5%.

Adverse Effects and Precautions

Topical application of benzoyl peroxide may produce skin irritation, particularly at the start of treatment. In some patients the irritation may require reduced frequency of application or temporary suspension of treatment. Skin dryness, peeling, rash, and transient local oedema may also occur. Contact sensitisation has been reported in some patients using preparations containing benzoyl peroxide. Caution is required when applying it near the eyes, the mouth and other mucous membranes, and to the neck and other sensitive areas. Patients should be alerted to benzoyl peroxide's bleaching property.

Body odour. An unusual unpleasant body odour in a patient was attributed to the topical use of benzoyl peroxide.[1]

1. Molberg P. Body odor from topical benzoyl peroxide. *N Engl J Med* 1981; 304: 1366.

Carcinogenicity. There has been concern at the implications of some *animal* studies showing benzoyl peroxide to possess some tumour-promoting activity.[1] However, a retrospective survey in Canada concluded that there was no indication that the normal use of benzoyl peroxide in the treatment of acne was associated with an increased risk of facial cancer.[2] A comprehensive review[3] that included *in-vitro* and *animal* studies, as well as human data, also concluded that there was no evidence to associate the topical use of benzoyl peroxide with the development of skin cancer in humans. However, the International Agency for Research on Cancer[4] considers that there is inadequate evidence in humans and its overall evaluation is that benzoyl peroxide is not classifiable as to its carcinogenicity to humans.

1. Jones GRN. Skin cancer: risk to individuals using the tumour promoter benzoyl peroxide for acne treatment. *Hum Toxicol* 1985; 4: 75–8.
2. Hogan DJ, *et al.* A study of acne treatments as risk factors for skin cancer of the head and neck. *Br J Dermatol* 1991; 125: 343–8.
3. Kraus AL, *et al.* Benzoyl peroxide: an integrated human safety assessment for carcinogenicity. *Regul Toxicol Pharmacol* 1995; 21: 87–107.
4. IARC/WHO. Benzoyl peroxide. *IARC monographs on the evaluation of carcinogenic risks to humans volume 71* 1999. Available at: http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf (accessed 27/09/07)

Handling. Benzoyl peroxide powder may explode if subjected to grinding, percussion, or heat. Hydrous benzoyl peroxide containing water to reduce the risk of explosion may still explode if exposed to temperatures higher than 60 degrees or cause fires in the presence of reducing substances.

Hypersensitivity. Benzoyl peroxide appears to induce contact hypersensitivity quite often when used to treat leg ulcers,[1] but it is unclear how often this occurs when used in the treatment of acne.[2] Patch testing[3,4] in some studies suggests that up to 76% of patients may be hypersensitive to benzoyl peroxide but this does not appear to correlate either with the clinical irritation produced during treatment, which usually resolves on continued use, or with the reported incidence of hypersensitivity.[2,4] In one study 25% of patients were considered to be hypersensitive from patch testing but only 2 of 44 patients developed clinical hypersensitivity.[4] Another study involving 204 patients with acne found that the incidence of false-positive irritant skin reactions to benzoyl peroxide was about 15% but only 1% of the patients had true allergic reactions to the drug on further testing.[5] However, there has been concern that hypersensitivity to benzoyl peroxide may be mistaken for irritation or worsening of the acne.[3]

1. Vena GA, *et al.* Contact dermatitis to benzoyl peroxide. *Contact Dermatitis* 1982; 8: 338.
2. Cunliffe WJ, Burke B. Benzoyl peroxide: lack of sensitization. *Acta Derm Venereol (Stockh)* 1982; 62: 458–9.
3. Leyden JJ, Kligman AM. Contact sensitization to benzoyl peroxide. *Contact Dermatitis* 1977; 3: 273–5.
4. Rietschel RL, Duncan SH. Benzoyl peroxide reactions in an acne study group. *Contact Dermatitis* 1982; 8: 323–6.
5. Balato N, *et al.* Acne and allergic contact dermatitis. *Contact Dermatitis* 1996; 34: 68–9.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies benzoyl peroxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pharmacokinetics

Work *in vitro* and in *animals*[1] suggests that although there is some absorption of benzoyl peroxide after topical application, any absorbed drug appears to be metabolised in the skin to benzoic acid and rapidly excreted in the urine.

1. Yeung D, *et al.* Benzoyl peroxide: percutaneous penetration and metabolic disposition II: effect of concentration. *J Am Acad Dermatol* 1983; 9: 920–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acnepas; Acnesan; Benzihex; Eclaran; Ecnagel PB; Paracne; PB Gel; Solugel; Tiltis; Valucne PB; Vixiderm E; Xicanil; *Austral.*: Benzac; Brevoxyl; Clearasil Ultra Acne Treatment Cream; Oxy; PanOxyl; *Austria*: Akneroxid; Benzaknen; Brevoxyl; *Belg.*: Akneroxid; Benzac; Brevoxyl; Pangel; *Braz.*: Acnase; Acnezil; Benzac AC; Benzac Dermesan; PanOxyl; Solugel; *Canad.*: Acetoxyl†; Acne Solutions; Acne Vanishing Treatment; Acneban; Adasept BP; Benoxyl†; Benzac; Benzagel; Cetaphil Acne; Clean & Clear Continuous Control; Clean & Clear Persa Gel; Clear Acne†; Clear Pore On-The-Spot†; Clear Skin Treatment Repairing; Clear Zone†; Clearasil Daily Clear Acne B.P. Plus; Clearasil Stayclear BP Plus†; Clenziderm; Dermacne; Dermalogica Special Clearing Booster; Desquam-X†; Emergency Acne; Life Acne; Medicated Acne Gel†; Nature's Cure Acne; Overnight Acne Control; Oxy†; Oxyderm; PanOxyl; Pure Perfection Classic; Rodan & Fields Proactiv Renewing Cleanser; Rodan & Fields Proactiv Repairing; Shave Cream; Skin ID; Solugel; Spectro Acnecare; *Chile*: Benzac; Pansulfox; Peroxiben Plus; Pirobac; Solugel; *China*: Benzihex (斑赛); Bi Ning (碧宁); *Cz.*: Akneroxid; Basiron AC†; Eclaran; Oxy†; *Denm.*: Basiron; *Fin.*: Basiron; Brevoxyl; *Fr.*: Brevoxyl; Curaspot; Cutacnyl; Eclaran; Effacne; Pannogel; PanOxyl; *Ger.*: Aknefug-oxid; Akneroxid; Benzaknen; Benzoyt; Benzperoxt; Brevoxyl; Cordes BPO; Klinoxid†; Marduk; PanOxyl; Sanoxit†; *Gr.*: Benzac-W; Bioacne; Brevoxyl; *Hong Kong*: Akneroxid; Benzac AC; Brevoxyl; Oxy†; Oxyderm†; PanOxyl; *Hung.*: Aknefug-oxid; Akneroxid; Lubexyl; *India*: Abenz; Actiben; Akneroxid; Benzac AC; Brevoxyl; Persol; *Indon.*: Benzolac; Pimplex†; *Irl.*: Acnecide; Brevoxyl; PanOxyl; *Israel*: Acne Derm; Benzac; Clearex Benzoyl Peroxide; Clearex Cover Up; Oxy; PanOxyl; *Ital.*: Benzac; Benzolait; PanOxyl; Reloxyl; *Malaysia*: Akneroxid; Benzac AC; Brevoxyl; PanOxyl; *Mex.*: Akeprul; Benoxyl; Benzac AC; Benzaderm; Solugel; *Neth.*: Akneroxid†; Benzac; Kruidvat Hydrogel; Oxy†; Tendox†; *Norw.*: Basiron; Brevoxyl†; PanOxyl†; *NZ*: Benzac; Brevoxyl; Clearasil Ultra; PanOxyl; *Phi-*

lipp.: Benoxyl†; Benzac AC; Brevoxyl†; PanOxyl; Ultra Clearasil†; *Pol.*: Akneroxid; Benzacne; Benzapur†; Brevoxyl; Lubexyl; *Port.*: Benoxygel; Benzac Eclaran; PanOxyl; Peroxiben; *Rus.*: Basiron (Базирон); Eclaran (Экларан); *S.Afr.*: Benoxyl†; Benzac AC; Brevoxyl; Clearasil Benzoyl P; Dry & Clear†; PanOxyl; *Singapore*: Acnacyl†; Akneroxid; Benzac; Brevoxyl; PanOxyl; *Spain*: Benoxygel†; Oxiderma; PanOxyl†; Peroxacne; Peroxiben; Soluclel; Stop Espinilla Normaderm†; *Swed.*: Basiron; Brevoxyl; Stioxyl†; *Switz.*: Acnefuge; Akneroxid; Aknex†; Benzac; Benzaknen; Lubexyl; *Thai.*: Acnexyl; Aczee; Benzac; Brevoxyl; Enzoxid; PanOxyl; *Turk.*: Aknefug BP; Aksil; Benzac AC; Neutrogena Acne Mask; *UK*: Acnecide; Brevoxyl; Oxy; PanOxyl; *USA*: Acne Clear; Acne Medication; Benzac; BenzE-Foam; Benziq; BP Gel; BP Wash; Brevoxyl; Clearasil; Clinac BPO; Del Aqua; Delos; Desquam; DesquamX; Postex; Lavoclen; NeoBenz; OC8; On-the-Spot Acne Treatment; Oxy; Pacnex; PanOxyl; Riax; SE BPO; Soluclenz; Triaz; Zaclir; *Venez.*: Acnex; Benzac AC; Ecuaderm; Neutrogena OnSpot.

Multi-ingredient Preparations. *Arg.*: Acnepas E; Clidan B; Clindacur; Clindoxyl; CP-Acne Duo; Dermaclean†; Duo Clindacin; Epiduo; Erimicin; Panalene Duo; Pentoclave Combi; Perclin; Peroxiclin Duo; Peroximicina; *Austral.*: ClindaBenz; Duac Epiduo; *Austria*: Acne Plus; Indoxyl; *Belg.*: Acneplus; Benzadermine; Benzamycin†; Epiduo; *Braz.*: Acnase; Clindoxyl; Epiduo; *Canad.*: Benzaclin; Benzamycin; Clindoxyl; Tactuo; *Chile*: Benzac Plus; Erimicin; Indoxyl; Klina; *China*: Benzamycin (必麦森); *Cz.*: Duac; *Denm.*: Clindoxyl; Epiduo; Tactuo†; *Fin.*: Clindoxyl; Epiduo; *Fr.*: Epiduo; *Ger.*: Acne Plus; Duac; Epiduo; *Gr.*: Benzamycin; Epiduo; Erybenz; Indoxyl; Zarcad; *Hong Kong*: Acnesol†; Benzolac Cl; Duac; Epiduo; *Hung.*: Duac; *India*: Acnebenz; Alesa; Persol Forte; *Indon.*: Benzolac Cl; Feldixid†; *Irl.*: Benzamycin†; Duac; Quinoderm; *Israel*: Benzaclin†; Benzamycin; Duac; *Ital.*: Acnidazil; Delta 80 Plus; Delta 80; Duac Epiduo; Katoxyn; *Malaysia*: Duac; *Mex.*: Benzac Plus†; Benzaclin†; Benzamycin†; Clindapack; Indoxyl; *Neth.*: Acnecare; Duac; *Norw.*: Epiduo; *NZ*: Duac; Epiduo; *Philipp.*: Acne Plus†; Duac; Epiduo; *Pol.*: Duac; Epiduo; *Port.*: Duac; Epiduo; Zacnet†; *S.Afr.*: Acnecleart; Acnidazil†; Quinoderm†; *Singapore*: Benzamycin†; Clindoxyl; Epiduo; *Spain*: Duac; Epiduo; Tactuoben; *Swed.*: Duac Epiduo; *Switz.*: Acne Creme Plus; Duac; Epiduo; *Thai.*: Duac; Epiduo; *Turk.*: Benzaclin; Benzamycin; Clindoxyl; *UK*: Duac Once Daily; Epiduo; Quinoderm; *Ukr.*: Duac (Дуак); *USA*: Acanya; Bencort; Benzaclin; Benzamycin; Duac; Effaclar Duo; Epiduo; Inova Acne Control; Inova; NuOx; Sulfoxyl; Vanoxide-HC; Zacare Kit; Zoderm.

Pharmacopoeial Preparations

BP 2014: Benzoyl Peroxide Cream; Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Potassium Hydroxyquinoline Sulphate and Benzoyl Peroxide Cream;

USP 36: Benzoyl Peroxide Gel; Benzoyl Peroxide Lotion; Erythromycin and Benzoyl Peroxide Topical Gel.

Bisoctrizole *(USAN, rINN)*

Bisoctrizol; Bisoctrizolum; FAT-75634; MBBT; Methylene Bis-Benzotriazolyl Tetramethylbutylphenol; Бизоктризол.

2,2′-Methylenebis[6-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol].

$C_{41}H_{50}N_6O_2$=658.9

CAS — 103597-45-1.

UNII — 8NT850T0YS.

NOTE. Tinosorb M is a trade name that has been used for bisoctrizole.

Pharmacopoeias. In *US*.

USP 36: (Bisoctrizole). Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Profile

Bisoctrizole is used as a sunscreen (p. 1681.3). It is effective against UVB and UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lelco; *Singapore*: Sunsense Anti-Ageing.

Multi-ingredient Preparations. *Arg.*: Fotocrem 50; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem UVA Plus†; Fotoprotector Extrem UVA†; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Pediatrics†; Fotoprotector Ultra; Fotosol Ultra 50; Fotosol Ultra Autobronceante; Fotosol Ultra; Fotosol; Lelco Ultrablock Extreme; Lelco Ultrablock†; Ocusun; Polysianes; Polysianes; Valublock V; Valublock; *Austral.*: Sunsense Anti Ageing Face; Sunsense Bronze Shield; Sunsense Ultra; *Braz.*: Fotoprotetor Isdin Extrem UVA†; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Extrem; *Canad.*: ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; *Chile*: Ansolar; Avene Spray 50+; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem Plus†; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotosol Cassara†; Fotosol Ultra†; Fotosol Ultra; Fotosol; Nutraisdin; Photoderm AKN†; Photoderm AR†; Photoderm Kid†; Photoderm Max†; Photoderm Spot†; Photoscreen†; Photoscreen; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; Uriage Crema Color; Uriage Crema Extra; Uriage Protector Solar†; *Fr.*: Avene Antirougeurs; Daylong; Hyseke Solaire; Melascreen solaire; SVR 100†; *Ger.*: Daylong actinica†; *Hong Kong*: Spectraban Sensitive 30; SunSense Anti-ageing Face Matte; *Malaysia*: SunSense Anti-Ageing Face; *Mex.*: Dermaglos Solar†; Eclipsol Clarity; Eclipsol Forte; Eclipsol Hydro; Eclipsol Ultra; ProZone Ultra Fluido; Umbrella Plus; *Singapore*: Protexio; *Switz.*: Daylong actinica; *UK*: Spotner; Uvistat; Uvistat; *Venez.*: Photoderm Max; Photoderm Max; Photoderm.

Calamine

Calamina; Kalamin; Prepared Calamine; Каламин.

Pharmacopoeias. In *Br., Chin., Int.*, and *US*.

BP 2014: (Calamine). It is a basic zinc carbonate coloured with ferric oxide. It is an amorphous, impalpable, pink or reddish-brown powder, the colour depending on the variety and amount of ferric oxide present and the process by which it is incorporated. Practically insoluble in water; it dissolves with effervescence in hydrochloric acid.

USP 36: (Calamine). It is zinc oxide with a small proportion of ferric oxide. A pink, odourless, fine powder. Insoluble in water; practically completely soluble in mineral acids.

Profile

Calamine has mild astringent and antipruritic actions and is used as a dusting powder, cream, lotion, or ointment in a variety of skin conditions although its value is uncertain.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Ducilamina; *India*: Calak: Intracal; *Spain*: Talquistina†; *Thai.*: Cabana.

Multi-ingredient Preparations. *Arg.*: Acuaderm; Caladryl; Calcusan; Dermithan; Irricutan; Labsacalm; Northicalm; Pinklot; Piracalamina; Prurisedan Rosa; Prurisedan; Urtikalma; *Austral.*: Animine; Calaband†; Calamine Lotion; Dermalife Plus†; *Belg.*: Caladryl; *Braz.*: Caladryl; Calamed; Calamina†; Calamyn; Calsol; Dermamina; Solardril Composto; *Canad.*: Aveeno Anti-Itch; Caladryl†; Calamine Antihistamine; Calmoseptine†; Lotion Calamine avec Antihistaminique; *Chile*: Ivarest; Prurived; *Fr.*: Gel de Calamine; Pruriced: Pruriced; *Hong Kong*: Aicadryl†; Bacamine†; Cadramine-V; DPH with Calamine†; Improved Versal†; Uni-Calmin†; Vasogen†; *India*: Calacare; Caladryl; Calak; Calosoft; Calskin; Calvera; Cimfi; Siloderm; *Indon.*: Caladine†; Caladryl†; Calamec†; Calarex†; Confortin; Minos†; Regata†; *Irl.*: RBC†; Vasogen†; *Israel*: Baby Paste + Chamomile†; Calamine Lotion; *Malaysia*: Dermoplex Calamine; Norash; Twinkle Calamine†; *Mex.*: Caladryl; Dermocare; Procicar; *NZ*: Am-O-Lin†; *Philipp.*: Caladryl; Calmoseptine; *Port.*: Benaderma com Calamina; Caladryl; *S.Afr.*: Adco-Blohist; Caladryl; Calasthetic; Histamed†; *Singapore*: Acne Clear; Calamine and Menthol; Calamol; Norash; *Thai.*: Allerdryl; Ancamin; Antipru; Cadinyl; Cadramine; Caladiph; Caladryl†; Calahyst Prx; Calakin; Calamine Lotion; Calamine Lotion; Calamine-D; Calanol; Calapro; Calarin; Caloryne; Canamine; Canerin; Clara; Fadril†; Hista; Kadryl; KB Calo; Lanol; M-D; Patar lotion; *Turk.*: Caladryl†; Derivit; Diyenil†; Kalmosan; Tanol; *UK*: Calaband; Lacto Calamine; Lacto Calamine; RBC; Swarm; Vasogen; *USA*: Aveeno Anti-Itch†; Caladryl; Calagesic; Calamycin; Dome-Paste; Ivarest; RA Lotion; *Venez.*: Borocanfor; Calaminol; Calasyl Original; Micofeet.

Pharmacopoeial Preparations

BP 2014: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Calamine Ointment;

USP 36: Calamine Topical Suspension; Phenolated Calamine Topical Suspension.

Calcipotriol *(BAN, rINN)*

Calcipotriene (USAN); Calcipotriolum; Kalcipotriol; Kalcypotriol; Kalsipotriol; Kalsipotrioli; MC-903; Кальципотриол.

(5*Z*,7*E*,22*E*,24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1α,3β,24-triol.

$C_{27}H_{40}O_3$=412.6

CAS — 112828-00-9; 112965-21-6.

ATC — D05AX02.

ATC Vet — QD05AX02.

UNII — 143NQ3779B.

Pharmacopoeias. In *Eur.* (see p. vii), which also includes the monohydrate.

Ph. Eur. 8: (Calcipotriol, Anhydrous; Calcipotriolum Anhydricum). A white or almost white, crystalline powder. It is sensitive to heat and light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers at a temperature of -20 degrees or below. Protect from light.

Ph. Eur. 8: (Calcipotriol Monohydrate; Calcipotriolum Monohydricum). A white or almost white, crystalline powder. It is sensitive to light. A reversible isomerisation to pre-calcipotriol takes place in solution, depending on temperature and time. The activity is due to both compounds. Practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in airtight containers. Protect from light.

Uses and Administration

Calcipotriol is a vitamin D_3 derivative. *In vitro* it appears to induce differentiation and to suppress proliferation of keratinocytes.

Calcipotriol is used in a cream or ointment for the management of plaque psoriasis and as a solution in the management of scalp psoriasis; the concentration of calcipotriol used is 0.005%. Applications should be made once or twice daily. No more than 100 g of cream or ointment, or 60 mL of scalp solution, should be applied in one week. If both are used, the limit is 60 g of cream or ointment with 30 mL of scalp solution, or 30 g of cream or ointment with 60 mL of scalp solution.

For the use of calcipotriol in children, see below.

Administration in children. Topical calcipotriol may be used in the management of plaque psoriasis in children. In the UK, the ointment (0.005%) may be applied twice daily. The maximum applied in one week should be 50 g in children aged 6 to 12 years, and 75 g in children more than 12 years of age. The *BNFC* also suggests that under specialist supervision the scalp solution (0.005%) may be applied twice daily to children aged 6 years and over for the treatment of scalp psoriasis; no more than 30 mL of the solution should be applied in one week to those aged 6 to 12 years, with older children receiving a maximum of 45 mL in one week. When preparations are used together, the *BNFC* recommends a maximum total calcipotriol dose of 2.5 mg in any one week for children aged 6 to 12 years (e.g. 20 mL of the scalp solution with 30 g of the ointment); in older children, the maximum is 3.75 mg in any one week (e.g. 30 mL of the scalp solution with 45 g of the ointment). In the UK, the scalp solution is not licensed for use in children and the ointment is not licensed for use in children under 6 years; however, safety and efficacy have been reported in small 8-week studies that have included children as young as 2 years old.[1-3] There are also a few case reports of topical calcipotriol use in infants with psoriasis, aged 3 months[4] and 6 months.[5]

1. Darley CR, *et al.* Safety and efficacy of calcipotriol ointment (Dovonex) in treating children with psoriasis vulgaris. *Br J Dermatol* 1996; 135: 390–3.
2. Oranje AP, *et al.* Topical calcipotriol in childhood psoriasis. *J Am Acad Dermatol* 1997; 36: 203–8.
3. Patrizi A, *et al.* Topical calcipotriol in childhood psoriasis. *Acta Derm Venereol* 1999; 79: 477.
4. Travis LB, Silverberg NB. Psoriasis in infancy: therapy with calcipotriene ointment. *Cutis* 2001; 68: 341–4.
5. Choi YJ, *et al.* Infantile psoriasis: successful treatment with topical calcipotriol. *Pediatr Dermatol* 2000; 17: 242–4.

Skin disorders. Topical drugs are the treatment of first choice for *chronic plaque psoriasis* (p. 1688.1). Calcipotriol, dithranol, and coal tar are commonly used for mild to moderate forms of the disorder. Calcipotriol inhibits cell proliferation and increases cell differentiation by binding to vitamin D receptors, thus inhibiting epidermal growth and returning some normality to the skin's structure. It is also possible that calcipotriol affects immunological and inflammatory processes in the skin.[1] Topical calcipotriol has been shown to be effective in mild to moderate chronic plaque psoriasis; it is at least as effective as dithranol, coal tar, and corticosteroids, and has been reported to be superior in several studies.[1,2] Calcipotriol is also more cosmetically acceptable than dithranol, which can stain, and coal tar, which can have an unpleasant smell. Benefits have been maintained with long-term use, and repeat courses are effective for the management of relapse. Although there are fewer studies in children, calcipotriol has been reported to be safe and effective in studies including children aged 2 to 15 years[1] (see also Administration in Children, above). Calcipotriol, applied as a topical solution, is also effective for *scalp psoriasis*.[3] When solutions of calcipotriol and betamethasone were compared for mild to moderate scalp psoriasis,[4] calcipotriol produced a satisfactory response, but betamethasone was more effective and was associated with less irritation of the scalp and face. Similar results were reported in a study comparing calcipotriol with clobetasol propionate in moderate to severe scalp psoriasis.[5] In a study of patients with *nail psoriasis* about half received benefit from calcipotriol ointment over a 3 to 5 month treatment period.[6] This result was similar to that found for patients treated with betamethasone and salicylic acid ointment.

Use of calcipotriol with other antipsoriatic drugs may be beneficial. The combination of calcipotriol with a topical corticosteroid is more effective than monotherapy with either of these.[1,7,8] Treatment for up to 4 weeks is usually effective and may be followed by maintenance calcipotriol monotherapy.[9] Topical calcipotriol with systemic therapies has also been tried. There is evidence that the response to oral ciclosporin or acitretin can be improved,[1] as can the response to phototherapy (UVB) or photochemotherapy (PUVA).[1,10] Combination therapy may also reduce the cumulative dose of acitretin, UVB, or PUVA required to achieve clearance or marked improvement of psoriasis, potentially reducing the risk of long-term adverse effects from these treatments.[1,10,11] However, because of the potential for the vehicle of topical calcipotriol preparations to block UV irradiation, they should be applied at least 2 hours before irradiation.[12] Despite promising reports from combination therapy using topical calcipotriol with systemic treatment, phototherapy, or photochemotherapy, a systematic review[13] found that although there can be a measurable additive effect, it may not be clinically significant in patients' own assessments.

A 2-week course of high-dose calcipotriol (up to 360 g of 0.005% ointment weekly) has been used for inpatient treatment of extensive psoriasis, followed by the usual recommended dose (up to 100 g weekly) for residual psoriasis.[14] Asymptomatic hypercalcaemia and hypercalciuria occurred in some patients, and the authors suggested that the monitoring of calcium homoeostasis is mandatory with this regimen (see also Effects on Calcium Homoeostasis, below). Relapse occurred in most patients within one year.

Beneficial results with calcipotriol have also been reported in small numbers of patients with various skin disorders[15] including *acrodermatitis continua of Hallopeau, confluent and reticulated papillomatosis, congenital ichthyosis, inflammatory linear verrucous epidermal nevus, lichen amyloidosis, morphea or linear scleroderma, pityriasis rubra pilaris, prurigo nodularis,* and *seborrhoeic dermatitis*. A small open study[16] has indicated that topical calcipotriol may be effective in the treatment of oral *leucoplakia* (see under Bleomycin, p. 750.3). It has also been tried, alone or with UVA or UVB, or a topical corticosteroid, in the treatment of *vitiligo*[17-21] (see Pigmentation Disorders, p. 1687.2), but results have been mixed.

1. Scott LJ, *et al.* Calcipotriol ointment: a review of its use in the management of psoriasis. *Am J Clin Dermatol* 2001; 2: 95–120.
2. Ashcroft DM, *et al.* Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis. *BMJ* 2000; 320: 963–7.
3. Thaçi D, *et al.* Calcipotriol solution for the treatment of scalp psoriasis: evaluation of efficacy, safety and acceptance in 3,396 patients. *Dermatology* 2001; 203: 153–6.
4. Klaber MR, *et al.* Comparative effects of calcipotriol solution (50 micrograms/mL) and betamethasone 17-valerate solution (1 mg/mL) in the treatment of scalp psoriasis. *Br J Dermatol* 1994; 131: 678–83.
5. Reygagne P, *et al.* Clobetasol propionate shampoo 0.05% and calcipotriol solution 0.005%: a randomized comparison of efficacy and safety in subjects with scalp psoriasis. *J Dermatol Treat* 2005; 16: 31–6.
6. Tosti A, *et al.* Calcipotriol ointment in nail psoriasis: a controlled double-blind comparison with betamethasone dipropionate and salicylic acid. *Br J Dermatol* 1998; 139: 655–9.
7. Fenton C, Plosker GL. Calcipotriol/betamethasone dipropionate: a review of its use in the treatment of psoriasis vulgaris. *Am J Clin Dermatol* 2004; 5: 463–78.
8. Kragballe K, van de Kerkhof PCM. Consistency of data in six phase III clinical studies of a two-compound product containing calcipotriol and betamethasone dipropionate ointment for the treatment of psoriasis. *J Eur Acad Dermatol Venereol* 2006; 20: 39–44.
9. White S, *et al.* Use of calcipotriene cream (Dovonex cream) following acute treatment of psoriasis vulgaris with the calcipotriene/betamethasone dipropionate two-compound product (Taclonex): a randomized, parallel-group clinical trial. *Am J Clin Dermatol* 2006; 7: 177–84.
10. Torras H, *et al.* A combination therapy of calcipotriol cream and PUVA reduces the UVA dose and improves the response of psoriasis vulgaris. *J Dermatol Treat* 2004; 15: 98–103.
11. Woo WK, McKenna KE. Combination TL01 ultraviolet B phototherapy and topical calcipotriol for psoriasis: a prospective randomized placebo-controlled clinical trial. *Br J Dermatol* 2003; 149: 146–50.
12. De Rie MA, *et al.* Calcipotriol ointment and cream or their vehicles applied immediately before irradiation inhibit ultraviolet B-induced erythema. *Br J Dermatol* 2000; 142: 1160–5.
13. Ashcroft DM, *et al.* Combination regimens of topical calcipotriene in chronic plaque psoriasis: systematic review of efficacy and tolerability. *Arch Dermatol* 2000; 136: 1536–43.
14. Bleiker TO, *et al.* Long-term outcome of severe chronic plaque psoriasis following treatment with high-dose topical calcipotriol. *Br J Dermatol* 1998; 139: 285–6.
15. Holm EA, Jemec GBE. The therapeutic potential of calcipotriol in diseases other than psoriasis. *Int J Dermatol* 2002; 41: 38–43.
16. Femiano F, *et al.* Oral leukoplakia: open trial of topical therapy with calcipotriol compared with tretinoin. *Int J Oral Maxillofac Surg* 2001; 30: 402–6.
17. Ameen M, *et al.* Topical calcipotriol as monotherapy and in combination with psoralen plus ultraviolet A in the treatment of vitiligo. *Br J Dermatol* 2001; 145: 476–9.
18. Chiaverini C, *et al.* Treatment of vitiligo by topical calcipotriol. *J Eur Acad Dermatol Venereol* 2002; 16: 137–8.
19. Kumaran MS, *et al.* Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *J Eur Acad Dermatol Venereol* 2006; 20: 269–73.
20. Goktas E, *et al.* Combination of narrow band UVB and topical calcipotriol for the treatment of vitiligo. *J Eur Acad Dermatol Venereol* 2006; 20: 553–7.
21. Arca E, *et al.* Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *J Dermatol* 2006; 33: 338–43.

Adverse Effects and Precautions

The most frequent adverse effect associated with calcipotriol is skin irritation and it should not therefore be applied to the facial area. Symptoms may include burning, itching, erythema, and dry skin, but stopping therapy is seldom necessary. Aggravation of psoriasis may occur. Hypercalcaemia has occurred during treatment with calcipotriol and although rapidly reversible on withdrawal, it should not be used in patients with disorders of calcium metabolism. Other rare adverse effects may include skin atrophy, hyperpigmentation, and photosensitivity. Patients should limit or avoid excessive exposure to both natural and artificial sunlight, because *animal* studies have suggested that topical calcipotriol may enhance the effect of UV radiation to induce skin tumours.

Effects on calcium homoeostasis. Calcipotriol is a vitamin D derivative and therefore has the potential to cause hypercalcaemia and hypercalciuria. Up to December 1993, when about 150 000 patients in the UK had been treated with calcipotriol, the UK CSM had received 6 reports of hypercalcaemia and 2 of hypercalciuria.[1] Three of the patients with hypercalcaemia either had used doses in excess of the recommended maximum (see Uses and Administration, p. 1697.3) or had pustular or exfoliative psoriasis. Hypercalcaemia and hypercalciuria were reversible on withdrawal of calcipotriol. A study[2] investigating the effect of calcipotriol on urine calcium excretion found that use of the maximum recommended dose for 4 weeks produced increased urine calcium excretion, and the authors suggested that patients requiring the maximum dose of calcipotriol should be monitored for hypercalciuria before and during treatment. A review[3] of the effects of vitamin D analogues on calcium homoeostasis concluded that patients with unstable psoriasis are at particular risk of toxicity from calcipotriol and that measurement of urine calcium excretion is a more sensitive indicator of toxicity than serum-calcium concentrations.

1. CSM/MCA. Dovonex ointment (calcipotriol). *Current Problems* 1994; 20: 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
2. Berth-Jones J, *et al.* Urine calcium excretion during treatment of psoriasis with topical calcipotriol. *Br J Dermatol* 1993; 129: 411–14.
3. Bourke JF, *et al.* Vitamin D analogues in psoriasis: effects on systemic calcium homeostasis. *Br J Dermatol* 1996; 135: 347–54.

Hyperpigmentation. Hyperpigmentation occurred at the site of calcipotriol application in 2 patients after use with PUVA-bath therapy (a topical psoralen with UVA irradiation) for psoriasis.[1] The effect persisted for at least 4 months in these patients. Hyperpigmentation of psoriatic plaques was also reported in a patient treated with topical calcipotriol and UVB phototherapy.[2] Abnormal lentiginous pigmentation of psoriatic plaques occurred in a patient treated with topical calcipotriol for psoriasis, which had worsened during chemotherapy for melanoma, and was still present 2 years after stopping chemotherapy and calcipotriol.[3] The authors also noted that melanoma can cause pigment changes and may have played a role in this case.

There has been some interest in the hyperpigmentary effects of calcipotriol for the possible treatment of vitiligo (see Skin Disorders, p. 1697.3).

1. Gläser R, *et al.* Hyperpigmentation due to topical calcipotriol and photochemotherapy in two psoriatic patients. *Br J Dermatol* 1998; 139: 148–51.
2. Rütter A, Schwarz T. Ausgeprägte Hyperpigmentierung in psoriatischen Plaques als Folge einer Kombinationsbehandlung mit UVB-311 nm und Calcipotriol. *Hautarzt* 2000; 51: 431–3.
3. Oláh J, *et al.* Pigment anomaly caused by calcipotriol in a subject with melanoma. *J Eur Acad Dermatol Venereol* 2004; 18: 113–15.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcipotriol as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Daivonex; *Austral.*: Daivonex; *Austria*: Psorcutan; *Belg.*: Daivonex; *Braz.*: Daivonex; *Canad.*: Dovonex; *Chile*: Daivonex; *China*: Aofuqing (澳夫青); Daivonex (达力士); Cz.: Daivonex; *Denm.*: Daivonex; Dovonex; *Fin.*: Daivonex; *Fr.*: Daivonex; *Ger.*: Daivonex; Psorcutan; *Gr.*: Cipocal; Dopotril; Dovonex; F-Psorin; Psoraffect; *Hong Kong*: Cipotriol; Daivonex; *Hung.*: Daivonex†; *India*: Daivonex; Hexitmar; *Indon.*: Daivonex; *Irl.*: Calcil†; Dovonex; *Israel*: Daivonex; *Ital.*: Daivonex; Psorcutan; *Jpn*: Dovonex; *Malaysia*: Daivobet; Daivonex; *Mex.*: Daivonex; Eukadar; *Neth.*: Daivonex†; Penipsorian†; *Norw.*: Daivonex†; *NZ*: Daivonex; *Philipp.*: Daivonex; *Pol.*: Daivonex; Sorel Plus; *Port.*: Daivonex; *Rus.*: Daivonex (Дайвонекс); *S.Afr.*: Dovonex; *Singapore*: Daivonex; *Spain*: Daivonex; *Swed.*: Daivonex†; *Switz.*: Daivonex; *Thai.*: Daivonex; *Turk.*: Psorcutan; *UK*: Dovonex; *USA*: Dovonex; Sorilux.

Multi-ingredient Preparations. *Arg.*: Taclonex; *Austral.*: Daivobet; *Austria*: Psorcutan Beta; Xamiol; *Belg.*: Dovobet; Xamiol; *Braz.*: Daivobet; *Canad.*: Dovobet; Xamiol; *China*: Daivobet (得肤宝); *Cz.*: Daivobet; Xamiol; *Denm.*: Daivobet; Xamiol; *Fin.*: Daivobet; Xamiol; *Fr.*: Daivobet; Xamiol; *Ger.*: Daivobet; Psorcutan Beta; Xamiol; *Gr.*: Dovobet; Xamiol; *Hong Kong*: Daivobet; Xamiol; *Hung.*: Daivobet; *India*: Daivobet; Hexitmar-B; *Indon.*: Daivobet; *Irl.*: Dovobet; Xamiol; *Israel*: Daivobet; Xamiol; *Ital.*: Dovobet; Token; Xamiol; *Mex.*: Daivobet; *Neth.*: Dovobet; Xamiol; *Norw.*: Daivobet; Xamiol; *NZ*: Daivobet; *Philipp.*: Daivobet; Xamiol; *Pol.*: Daivobet; Xamiol; *Port.*: Daivobet; Xamiol; *Rus.*: Daivobet (Дайвобет); *S.Afr.*: Dovobet; *Singapore*: Daivobet; Xamiol; *Spain*: Daivobet; Xamiol; *Swed.*: Daivobet; Xamiol; *Switz.*: Daivobet; Xamiol; *Thai.*: Daivobet; Xamiol; *Turk.*: Psorcutan Beta; *UK*: Dovobet; Xamiol†; *USA*: Taclonex.

Centella

Azijinės centelės žolė; Ázsiai gázlófű; Centellae Asiaticae Herba; Herba Centellae; Hidrocótilo; Hydrocotyle; Indian Pennywort; Naťcentely asijské; Rohtosammakonputki; Sallatsspikblad; Wassernabelkraut, Asiatisches; Центелла Азиатская (*Centella asiatica*).

CAS — 464-92-6 (asiatic acid); 16830-15-2 (asiaticoside); 18449-41-7 (madecassic acid); 34540-22-2 (madecassoside).

ATC Herb — HM01AW5005 (Centella asiatica: *herb*); *HD03WB5001* (Centella asiatica: *herb*).

UNII — 7M867G6T1U (Centella asiatica); *6810070TYD* (Centella asiatica *extract*).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii) and *US*. *US* also includes a powdered form, a powdered extract, and Centella Asiatica Triterpenes.

Ph. Eur. 8: (Centella). The dried, fragmented aerial parts of *Centella asiatica*. It contains not less than 6% of total triterpenoid derivatives, expressed as asiaticoside, calculated with reference to dried drug. Protect from light.

USP 36: (Centella Asiatica). The dried aerial parts of *Centella asiatica* (*Hydrocotyle asiatica*) (Apiaceae). It is also known in commerce as gotu kola. It contains not less than 2.0% of triterpene derivatives. Protect from light and moisture.

USP 36: (Centella Asiatica Triterpenes). A fraction enriched in *Centella asiatica* triterpenes derivatives. It contains not less than 90.0% of triterpene derivatives. Store at a temperature of 20 degrees to 25 degrees, excursions permitted between 15 degrees and 30 degrees. Protect from light and moisture.

Profile

Centella contains the triterpene acids madecassic acid, asiatic acid, and their glycosides asiaticoside and madecassoside. It has been used topically and orally in the management of wounds, ulcers, and keloid scars. Preparations containing asiaticoside and madecassoside have also been used.

The names gotu kola, gotu cola, and gota kola are used for *Centella asiatica* (=*Hydrocotyle asiatica*) in herbal medicine.

Homoeopathy

Centella has been used in homoeopathic medicines.

References.
1. WHO. Herba Centellae. *WHO Monographs on Selected Medicinal Plants.* volume 1. Geneva: WHO; 1999. Also available at: http://apps.who.int/medicinedocs/en/d/Js2200e/10.html (accessed 27/05/10)

Adverse effects. Contact dermatitis has been reported with the topical use of centella.[1] There is also a report of 3 cases of hepatotoxicity associated with ingestion of centella, all presenting with jaundice, painful hepatomegaly, and granulomatous hepatitis with areas of necrosis.[2]

1. Gonzalo Garijo MA, *et al.* Allergic contact dermatitis due to Centella asiatica: a new case. *Allergol Immunopathol (Madr)* 1996; 24: 132–4.
2. Jorge OA, Jorge AD. Hepatotoxicity associated with the ingestion of Centella asiatica. *Rev Esp Enferm Dig* 2005; 97: 115–24.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Pertusan; *Belg.*: Madecassol; *Braz.*: Centelax†; Centella-Vit†; *Chile*: Celulase Plus; Celulase; Centabel; Escar T; Madecassol; *Fr.*: Madecassol; *Gr.*: Madecassol; *Hong Kong*: Madecassol; *India*: Iqmem; Learnol Plus; *Indon.*: Fitocassol; Lanakeloid; Madecassol; Tekasol; *Ital.*: Centellase; *Malaysia*: Lanakeloid; *Mex.*: Madecassol; *Port.*: Madecassol; *Singapore*: Centellase; Centica; Lanakeloid; *Spain*: Blastoestimulina; Grail; *Thai.*: Madecassol; *Turk.*: Madecassol; *Venez.*: Litonate; Madecassol.

Multi-ingredient Preparations. *Arg.*: Adelgazar; Aftersun; Biocell; Cellasene Gold; Cellasene†; Celu-Atlas; Centella Asiatica Compuesta; Centella Asiatica Diates†; Centella Asiatica Plus; Centella Asiatica Spir; Centella Asiatica Vital; Centella Incaico; Centella Queen Complex; Centella Queen Complex; Centella Queen Reductora; Centellacrom; Centellase de Centella Queen; Cen-

tellase Gel; Clevosan; Clevosan; CVP Cellulite; CVP Cellulite; Desgras Piel Naranja; Doctor 10 Body; Durgel; Energizante Vital con ginseng; Estri-Atlas; Fangan Plus; Garcinol Max; Gentianella; Ginal Cent; Ginkan; Herbaccion Ceifin; Indian Health - Centella; Indian Health - Garcinia; Linfol Cicatrizante; Lociherp Liposomas Antiage; Lociherp Liposomas Vitaminado; Mailen; Moragen; Natural Diet; Neo Pelvicillin; Nlo Marine; No-Gras; Ovufem; Ovumix; Pentol; Redudiet; Septigyn; Vagicural Plus; Varicura; Venoful; VNS 45; *Austral.*: Aesculus & Ruscus Compound; Arthro-Eze; Brahmi Super Learning Complex; Extralife Leg-Care†; For Women Active Woman Formula†; Mindac; *Chile*: Cellenergy; Celu-Atlas; Celulase Con Neomicina; Cicaplast; Cicapost; Escar T-Neomicina; Estri-Atlas; Perfect Body; Redermic Piel; Redermic XL; Ruboril AI; Ureadin Rx DB; *Fr.*: Cicaplast; Cicatridine; Fadiamone; Veganix; *Ger.*: Ialunara; *India*: Abana; Attentio; Dermec; Dermec; Geriforte; Geriforte; Memtone; Menosan; Mentat; Mulmin Plus; *Indon.*: Lanakeloid-E; Venos; *Ital.*: Angiorex Complex; Angioton; Angioton; Angiovein; Capill Venogel; Capill; Centella Complex; Centella Complex; Centeril H; Centeril H; Clebolider†; Criotonal; Dermilia Flebozin†; Emmenoiasi; Flavion; Flebo-Si†; Flebofort; Flebofort; Flebolider; Flebovis; Flebozin; Fraxiven; Gelovis; Idren; Levital Plus; Lik-Gel†; Neomyrt Plus; Osmogel; Pik Gel; Proctocella Complex; Slimmer Plus; Tractoven; Vaginol; Vasotonal; Venactive; Venoplant; Venoplant; Venoplant; Wasotonal†; *Malaysia*: Lanakeloid-E; *Mex.*: Madecassol C; Madecassol N; Nordibela; Varicyl; *Mon.*: Akildia; Cicaleine; *Philipp.*: Memory DD†; Memory Plus; Premium Memori Plus; Ruflex; *Port.*: Antiestrias; *Singapore*: Lanakeloid-E; Memomet; Ruflex; *Spain*: Blastoestimulina†; Blastoestimulina; Blastoestimulina; Cemalyt; Nesfare; *Ukr.*: Intellan (Интелла); Osteoartisi Max (Остеоартизи Макс); Trypsidan (Трипсидан)†; *USA*: Mucotrol; *Venez.*: Celyth's.

Homoeopathic Preparations. *Fr.*: Boripharm No 1†; Boripharm No 22†; Saponaria Compose; *Ger.*: Allergo-Loges; Cefabene Cistus Komplex†; Cistus canadensis Oligoplex; Ekzevowen.

Ceramides

N-Acylsphingosines.

CAS — 104404-17-3 (ceramide); 100403-19-8 (ceramides).

Profile

Ceramides are a diverse group of sphingolipids found in the skin. They consist of a sphingoid base (sphingosine, phytosphingosine, or hydroxysphingosine) linked to a fatty acid by an amide bond; the fatty acid may be an alpha hydroxy acid, an esterified alpha hydroxy acid, or a nonhydroxy acid and the carbon chains vary in length but usually contain between 16 and 40 carbon atoms. The major ceramides present in human skin have been classified either by their characteristics on chromatography (ceramides 1 to 8) or by a code consisting of 1 or 2 letters defining the type of fatty acid (A, EO, or N) followed by a letter defining the sphingoid base (S, P, or H).

Ceramides have an important role in the structure and function of the stratum corneum and natural and synthetic ceramides and their precursors have been applied topically in skin disorders such as dry skin and eczema. They have also been given orally in nutritional supplements.

Reviews.

1. Coderch L, *et al.* Ceramides and skin function. *Am J Clin Dermatol* 2003; 4: 107–29.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Philipp.*: Ceraklin.

Multi-ingredient Preparations. *Arg.*: Aminoterapia†; Lipiforce; Ureadin Facial; *Chile*: Effaclar H; Ureadin Facial Antiarrugas; Ureadin Facial; Urealeti: *Fr.*: Actipur 3 en 1; Actipur Antiimperfections; *Hong Kong*: Physiogel; *Malaysia*: Pynocare-white; *Singapore*: Balneum Intensiv; Ceradan; *UK*: Balneum.

Cerous Nitrate

Cerio, nitrato de; Cerium Nitrate; Ceru(III) azotan; Церия Нитрат.

$Ce(NO_3)_3$=326.1

CAS — 10108-73-3.

UNII — 7U25VKD7PW.

Profile

Cerous nitrate has been used topically, mainly with sulfadiazine silver, in the treatment of burns.

References.

1. Garner JP, Heppell PS. Cerium nitrate in the management of burns. *Burns* 2005; 31: 539–47.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Flammacerium; *Braz.*: Dermacerium; *Fr.*: Flammacerium; *Gr.*: Flammacerium; *Hong Kong*: Flammacerium; *Neth.*: Flammacerium; *Philipp.*: Flammacerium; *Pol.*: Flammacerium†; *Spain*: Flammazine Cerio; *UK*: Flammacerium.

Cinnamates

Cinnamate Esters.

Profile

Cinnamates are esters of cinnamic acid (p. 1748.3). Simple esters such as ethyl cinnamate (p. 2185.1) are used as flavours and perfumes. Substituted cinnamates, including *p*-methoxycinnamates such as octinoxate (p. 1715.1), are used as sunscreens.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Avene 20 Proteccion Total; Avene 20 Proteccion Total; Fotoprotectores; Fotoprotectores; Photoscreen†; Photoscreen; *Fr.*: SVR 100†; *Port.*: Uriage Extreme†.

Cinoxate *(USAN, rINN)*

Cinoxato; Cinoxatum; Циноксат.

2-Ethoxyethyl *p*-methoxycinnamate; 3-(4-Methoxyphenyl)-2-propenoic acid 2-ethoxyethyl ester.

$C_{14}H_{18}O_4$=250.3

CAS — 104-28-9.

UNII — 5437O7N5BH.

Profile

Cinoxate, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: RV Paque; *Venez.*: Neutrogena Ultra Sheer.

Crilanomer *(rINN)*

Acrylonitrile-starch Copolymer; Crilanomère; Crilanómero; Crilanomerum; ZK-94006; Крилановер.

A starch polymer with acrylonitrile.

CAS — 37291-07-9.

ATC — D03AX09.

ATC Vet — QD03AX09.

Profile

Crilanomer is a starch copolymer used as a hydrogel wound dressing in the management of wounds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Intrasite.

Crotamiton *(BAN, rINN)*

Crotam; Crotamitón; Crotamitonum; Krotamiton; Krotamitonas; Krotamitoni; Кротамитон.

N-Ethyl-*N*-*o*-tolylcrotonamide; *N*-Ethylcrotono-*o*-toluidide; *N*-Ethyl-*N*-(2-methylphenyl)-2-butenamide.

$C_{13}H_{17}NO$=203.3

CAS — 483-63-6.

ATC Vet — QP53AX04.

UNII — D6S4O4XD0H.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Crotamiton). A colourless or pale yellow oily liquid. It solidifies partly or completely at low temperatures. It is mainly the (*E*)-isomer, with not more than 15% of the (*Z*)-isomer. Slightly soluble in water; miscible with alcohol. Protect from light.

USP 36: (Crotamiton). A colourless to slightly yellowish oil with a faint amine-like odour. It is a mixture of *cis*- and *trans*-isomers. Soluble in alcohol and in methyl alcohol. Store in airtight containers. Protect from light.

Uses and Administration

Crotamiton is used as an antipruritic (p. 1687.3), although its value is considered uncertain (see also below). It is applied as a 10% cream or lotion 2 or 3 times daily; children aged less than 3 years may receive one application daily.

Crotamiton has also been used as an acaricide in the treatment of scabies but other more effective drugs are usually preferred (p. 2148.1). The 10% cream or lotion is applied, after first bathing and drying, to the whole of the body-surface below the chin, particular attention being paid to body folds and creases. A second application should be applied 24 hours later but it may need to be used once daily up to a total of 5 days to be effective.

Pruritus. A double-blind study in 31 patients[1] found that 10% crotamiton lotion was no more effective an antipruritic than its vehicle.

1. Smith RB, *et al.* Crotamiton lotion in pruritus. *Int J Dermatol* 1984; 23: 684–5.

Adverse Effects and Precautions

Topical use of crotamiton occasionally causes irritation. There have been rare reports of hypersensitivity reactions. Crotamiton should not be used in patients with acute exudative dermatitis. It should not be applied near the eyes, mouth, or other mucous membranes or on excoriated skin.

Ingestion of crotamiton may cause burning and irritation of oral, oesophageal, and gastric mucosa with nausea, vomiting, and abdominal pain.

Overdosage. A 23-year-old woman developed tonic-clonic seizures, requiring treatment with diazepam, after ingestion of a crotamiton emulsion.[1] Other hospital treatment included gastric lavage, activated charcoal, and metoclopramide. Crotamiton was detected in serum at a concentration of 34 micrograms/mL and was also detectable with several metabolites in the urine. Reference was also made to a report of a 2½-month-old child who had developed pallor and cyanosis after excessive dermal application of a crotamiton cream.

1. Meredith TJ, *et al.* Crotamiton overdose. *Hum Exp Toxicol* 1990; 9: 57.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Eurax; *Austria*: Eurax†; *Belg.*: Eurax†; *Canad.*: Eurax; *Chile*: Eurax; *China*: An Fu Kang (安夫康); Youlifu (优力肤); *Fr.*: Eurax; *Ger.*: Crotamitex†; Eraxil†; *Gr.*: Eurax; *Hong Kong*: Dermorax†; Eurax; Eurosin; Marax†; *India*: Crotorax; *Irl.*: Eurax; *Israel*: Eurax; Scabicin; *Ital.*: Eurax; *Malaysia*: A-Bite; Crotorax†; Eurax; Moz-Bite; *Mex.*: Acomexol; Eurax; *Norw.*: Eurax; *NZ*: Eurax; Itch-Soothe; *Philipp.*: Congen; Eurax; Scabirax†; *Port.*: Eurax; Scabicin; *S. Afr.*: Eurax; *Singapore*: Crotorax; Eurax; Moz-Bite; *Switz.*: Eurax; *UK*: Eurax; *USA*: Eurax; *Venez.*: Crotanol.

Multi-ingredient Preparations. *Arg.*: Anastim; Empecid Pie; *Chile*: Kertyol; *Fr.*: Kelual DS; *Hong Kong*: Uni-Rax-HC†; *India*: Crotorax-HC; Kertyol-S; *Irl.*: Eurax-Hydrocortisone; *Israel*: Duo-Scabil; *Jpn*: Una A Gel†; Una A; *Malaysia*: Crotamiton H; *Singapore*: Crotorax-HC; *UK*: Eurax Hc; *Venez.*: Kertyol.

Pharmacopoeial Preparations

BP 2014: Crotamiton Cream; Crotamiton Lotion;
USP 36: Crotamiton Cream.

Dextranomer *(BAN, rINN)*

Dekstranomeeri; Dextranomère; Dextranómero; Dextranomerum; Декстраномер.

Dextran cross-linked with epichlorohydrin (1-chloro-2,3-epoxypropane); Dextran 2,3-dihydroxypropyl 2-hydroxy-1,3-propanediyl ether.

CAS — 56087-11-7.

ATC — D03AX02.

ATC Vet — QD03AX02.

UNII — 30KXI0TVD3.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dextranomer). White or almost white, spherical beads. Practically insoluble in water. It swells in water and electrolyte solutions

Uses and Administration

The action of dextranomer as a wound dressing depends upon its ability to absorb up to 4 times its weight of fluid, including dissolved and suspended material of molecular weight up to about 5000.

Dextranomer is used for the cleansing of exudative and infected burns (p. 1683.1), wounds and ulcers (p. 1690.1), and for preparation for skin grafting.

The wound is cleansed with sterile water or saline and allowed to remain wet; dextranomer in the form of spherical beads is sprinkled on to a depth of at least 3 to 6 mm and covered with a sterile dressing. Occlusive dressings are not recommended as they may lead to maceration around the wound. The dextranomer should be removed when the

layer has become saturated with exudate; the old layer is washed off with a stream of sterile water or saline before renewal. The frequency of renewal will depend on the wound, ranging from once or twice daily to several times a day. All dextranomer must be removed before skin grafting. Dextranomer may also be applied as a paste (either ready-made or prepared by mixing dextranomer beads with glycerol).

Implants containing dextranomer microspheres in a stabilised hyaluronic acid carrier gel (NASHA/Dx) have been injected into the submucosa of the urethra in the management of female stress urinary incontinence (p. 2349.2). Connective tissue gradually surrounds the microspheres, and the resulting augmented tissue helps to restore urinary continence. In vesicoureteral reflux in children, implants containing up to 50 mg may be injected into the submucosa of the ureter, creating a bulge close to the ureteral orifice. The procedure may be repeated after 3 months if necessary.

References.
1. Stenberg ÅM, *et al.* Urethral injection for stress urinary incontinence: long-term results with dextranomer/hyaluronic acid copolymer. *Int Urogynecol J* 2003; 14: 335–8.
2. van Kerrebroeck P, *et al.* Efficacy and safety of a novel system (NASHA/Dx copolymer using the Implacer device) for treatment of stress urinary incontinence. *Urology* 2004; 64: 276–81.
3. Chapple CR, *et al.* An open, multicentre study of NASHA/Dx Gel (Zuidex®) for the treatment of stress urinary incontinence. *Eur Urol* 2005; 48: 488–94.
4. Dean GE, Doumanian LR. The extended use of Deflux (dextranomer/hyaluronic acid) in pediatric urology. *Curr Urol Rep* 2006; 7: 143–8.
5. Routh JC, *et al.* Single center experience with endoscopic management of vesicoureteral reflux in children. *J Urol (Baltimore)* 2006; 175: 1889–93.
6. Yu RN, Roth DR. Treatment of vesicoureteral reflux using endoscopic injection of nonanimal stabilized hyaluronic acid/dextranomer gel: initial experience in pediatric patients by a single surgeon. *Pediatrics* 2006; 118: 698–703.
7. Mollitierno JA, *et al.* Endoscopic treatment of vesicoureteral reflux using dextranomer hyaluronic acid copolymer. *J Pediatr Urol* 2008; 4: 221–8.

Adverse Effects and Precautions

Dextranomer can cause pain during dressing changes in some patients, and bleeding, blistering, and erythema have been reported occasionally. It should not be used in deep wounds or cavities from which it cannot be easily removed, nor should it be used on dry wounds. Care should be exercised when paste formulations of dextranomer are used near the eyes.

Spillage may render surfaces very slippery.

Viscous gel implants containing dextranomer, injected submucosally around the urethra, can cause transient urinary retention. Injection site reactions including mass, abscess, and pseudocyst formation have been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Debrisan; *Mex.*: Debrisan; *Pol.*: Acudex†; *S.Afr.*: Debrisan†; *USA*: Debrisan†.

Multi-ingredient Preparations. *UK*: Zuidex; *USA*: Deflux; Solesta.

Dibenzoylmethane

Dibenzoilmetano; Дибензоилметан.
1,3-Diphenyl-1,3-propanedione.
$C_{15}H_{12}O_2$=224.3
CAS — 120-46-7.
UNII — ANS7ME8OKC.

Profile

Dibenzoylmethane is a sunscreen (p. 1681.3) with actions similar to those of avobenzone (p. 1695.1). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *UK*: RoC Sunscreen Stick.

Dihydroxyacetone

Cetotriosa; DHA; Dihidroxiacetona; Ketotriose; Дигидроксиацетон.
1,3-Dihydroxypropan-2-one.
$C_3H_6O_3$=90.08
CAS — 96-26-4.
UNII — O10DDW6JOO.

NOTE. DHA is also used as a synonym for docosahexaenoic acid (p. 1460.1).

Pharmacopoeias. In *US*.

USP 36: (Dihydroxyacetone). A white to off-white crystalline powder. The monomeric form is freely soluble in water, in alcohol, and in ether; the dimeric form is freely soluble in water, soluble in alcohol, and sparingly soluble in ether. A 5% solution in water has a pH between 4.0 and 6.0. Store at a temperature of 8 degrees to 15 degrees in airtight containers.

Uses and Administration

Application to the skin of preparations containing dihydroxyacetone slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin.

A single application may give rise to a patchy appearance; progressive darkening of the skin results from repeated use until a point is reached when the maximum effect is achieved. If the treatment is stopped the colour starts to fade after about 2 days and disappears completely within 8 to 14 days as the external epidermal cells are lost by normal attrition.

Preparations usually contain 5% of dihydroxyacetone and have been used to camouflage vitiligo (see Pigmentation Disorders, p. 1687.2) or to produce an artificial suntan. Some preparations include sunscreens since the pigmentation produced gives no protection against sunburn.

Adverse Effects and Precautions

Skin irritation from dihydroxyacetone occurs rarely; rashes and allergic dermatitis have been reported. Contact with eyes, abraded skin, and clothing should be avoided.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Autohelios Bronz; DHA Autobronceante; Eurocolor Sin Sol; Ikx Autobronceante†; Leico sin Sol; Maprosol Autobronceante; *Austral.*: Tru Bronz; Vitadye†; *Braz.*: Autohelios; *Chile*: Fotoprotectores; Leche Autobronceante; Neutrogena Build a Tan; ROC Minesol Bronze; Uriage Bruma Autobronceante; *Mex.*: Dermacrom; *USA*: Chromelin Complexion Blender.

Multi-ingredient Preparations. *Arg.*: Fotosol Ultra Autobronceante; Polysianes Autobronceante; *Austral.*: Sunsense Self Tanning System Self Tan; *Braz.*: Sunmax Autobronzeador; *Chile*: Neutrogena Build a Tan; *Fr.*: Autohelios; Viticolor; *UK*: ViTicolor; *USA*: QT.

Diolamine Methoxycinnamate

DEA-Methoxycinnamate; Diethanolamine Methoxycinnamate; Diolamina metoxicinnamato; Diolamine Méthoxycinnamate; Diolamine *p*-Methoxycinnamate (pINNM); Diolaminum Metoxicinnamatum; Диоламин Метоксисинамат.
p-Methoxycinnamic acid compound with 2,2'-iminodiethanol (1:1).
$C_{10}H_{10}O_3.C_4H_{11}NO_2$=283.3
CAS — 56265-46-4.
UNII — 1UFJ6AS9NX.

Profile

Diolamine methoxycinnamate, a compounded substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (p. 1715.1). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: President's Choice Sunblock.

Dioxybenzone (*USAN, rINN*)

Benzofenon-8; Benzophenone-8; Dioxibenzona; Dioxybenzonum; NSC-56769; Диоксибензон.
2,2'-Dihydroxy-4-methoxybenzophenone.
$C_{14}H_{12}O_4$=244.2
CAS — 131-53-3.
UNII — B762XZ551X.

Pharmacopoeias. In *US*.

USP 36: (Dioxybenzone). A yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Dioxybenzone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Solaquin Forte; Spectraban *Canad.*: Solaquin Forte; *Chile*: Clasifel; *Mex.*: Clasifel; *USA* Solaquin Forte; Solaquin Forte.

Pharmacopoeial Preparations
USP 36: Dioxybenzone and Oxybenzone Cream.

Diphencyprone

Difenciprona; Дифенципрон.
2,3-Diphenylcyclopropenone-1.
$C_{15}H_{10}O$=206.2
CAS — 886-38-4.
UNII — I7G14NW5EC.

Profile

Diphencyprone has been applied as a contact sensitiser for the treatment of alopecia. It has also been tried in warts.

Adverse effects. Diphencyprone is considered to lack serious adverse effects but some patients may not be able to tolerate the induced hypersensitivity reaction. There have been reports of generalised urticaria and dermographism, sometimes severe, following the use of diphencyprone.[1-5] In another case, a severe reaction of urticaria and dermographism, which lasted several months, occurred after the initial sensitisation dose.[6] Allergy to diphencyprone has been reported in medical and nursing staff in spite of taking protective precautions during its application.[7] A patient who received diphencyprone treatment for warts developed a widespread pruritic rash and palpitations due to ventricular extrasystoles.[1] Vitiligo has also been reported in patients treated with diphencyprone[8-10] and it has been suggested that this might be due to unmasking of subclinical vitiligo.[8,9] Erythema multiforme-like eruptions have been associated with the topical application of diphencyprone.[11,12]

1. Lane PR, Hogan DJ. Diphencyprone. *J Am Acad Dermatol* 1988; 19: 364–5.
2. Tosti A, *et al.* Contact urticaria during topical immunotherapy. *Contact Dermatitis* 1989; 21: 196–7.
3. Skrebova N, *et al.* Severe dermographism after topical therapy with diphenylcyclopropenone for alopecia universalis. *Contact Dermatitis* 2000; 42: 212–15.
4. Francomano M, Seidenari S. Urticaria after topical immunotherapy with diphenylcyclopropenone. *Contact Dermatitis* 2002; 47: 310–11.
5. Short KA, Higgins EM. Urticaria as a side-effect of diphencyprone therapy for resistant viral warts. *Br J Dermatol* 2005; 152: 583–5.
6. Alam M, *et al.* Severe urticarial reaction to diphenylcyclopropenone therapy for alopecia areata. *J Am Acad Dermatol* 1999; 40: 110–12.
7. Shah M, *et al.* Hazards in the use of diphencyprone. *Br J Dermatol* 1996; 134: 1153.
8. Hatzis J, *et al.* Vitiligo as a reaction to topical treatment with diphencyprone. *Dermatologica* 1988; 177: 146–8.
9. Duhra P, Foulds IS. Persistent vitiligo induced by diphencyprone. *Br J Dermatol* 1990; 123: 415–16.
10. Henderson CA, Ilchyshyn A. Vitiligo complicating diphencyprone sensitization therapy for alopecia universalis. *Br J Dermatol* 1995; 133: 496–7.
11. Perrei CM, *et al.* Erythema multiforme-like eruptions: a rare side effect of topical immunotherapy with diphenylcyclopropenone. *Dermatologica* 1990; 180: 5–7.
12. Oh C-W, *et al.* Bullous erythema multiforme following topical diphenylcyclopropenone application. *Contact Dermatitis* 1998; 38: 220–1.

Alopecia. Diphencyprone has been used as a contact sensitiser in the treatment of various forms of alopecia (p. 1682.3) including areata, totalis, and universalis. Case series reports generally describe treatment of adults, but some groups have also included adolescents and children, and some have reported solely on treatment in children.[1,2]

Initial sensitisation is usually achieved by applying a 2% solution of diphencyprone in acetone to a small area of scalp, which may be repeated if necessary beneath plastic occlusion if adequate sensitisation is not produced. Thereafter, weaker concentrations are applied once weekly and gradually increased in strength to produce erythema and pruritus for 36 to 48 hours post-therapy. Concentrations that have been used vary between reports and the first treatment application may be as dilute as 0.00001%, with further applications gradually increased to up to 2%. Only one side of the scalp is treated until the optimum concentration is found, in order to prevent a widespread adverse reaction. Once hair regrowth has started on the treated side the applications may be extended to the entire scalp.[1-8] As well as erythema and pruritus, patients usually have transient eczema and regional lymph node swelling.[2,5,7,8]

Hair regrowth may not start for several months,[4,6,8] and the required duration of therapy can vary considerably; at least 8 months of treatment may be required,[3,6] and up to 12 months[1,2] or more[4,6] has been reported. Not all patients will respond to treatment and reported response rates vary, although these have probably been influenced by the different definitions used for complete, partial, and no response. Overall, however, regrowth of hair can occur in

up to about 70% of patients, with around half of these having complete regrowth.[1,4,6-8] Some reports have attempted to determine which factors might be associated with clinical response to diphencyprone. There is disagreement between studies but some possible unfavourable prognostic factors include extensive involvement,[4,6,8] younger age at onset,[8] longer disease duration before treatment,[5,7] and a history of atopic eczema.[4,7] The need for high diphencyprone concentrations and prolonged therapy have also been associated with a less favourable outcome.[8]

Despite these rates of response a significant number of patients will relapse, either during or after stopping treatment, and re-treatment may be considered.[4,6,7] The time to relapse can be variable. Remission in a small group of complete responders ranged from 1 month to 2 years after stopping therapy.[4] Another group of patients who achieved total regrowth of hair were able to stop treatment with diphencyprone for a mean of 15 months without relapse[9] while a further group maintained satisfactory hair growth for a mean follow-up period of 19.8 months.[5]

1. MacDonald Hull S, *et al.* Alopecia areata in children: response to treatment with diphencyprone. *Br J Dermatol* 1991; 125: 164–8.
2. Schuttelaar M-L, *et al.* Alopecia areata in children: treatment with diphencyprone. *Br J Dermatol* 1996; 135: 581–5.
3. MacDonald Hull S, Cunliffe WJ. Successful treatment of alopecia areata using the contact allergen diphencyprone. *Br J Dermatol* 1991; 124: 212–13.
4. Hoting E, Boehm A. Therapy of alopecia areata with diphencyprone. *Br J Dermatol* 1992; 127: 625–9.
5. Gordon PM, *et al.* Topical diphencyprone for alopecia areata: evaluation of 48 cases after 30 months' follow-up. *Br J Dermatol* 1996; 134: 869–71.
6. Pericin M, Trüeb RM. Topical immunotherapy of severe alopecia areata with diphenylcyclopropenone: evaluation of 68 cases. *Dermatology* 1998; 196: 418–21.
7. Cotellessa C, *et al.* The use of topical diphenylcyclopropenone for the treatment of extensive alopecia areata. *J Am Acad Dermatol* 2001; 44: 73–6.
8. Wiseman MC, *et al.* Predictive model for immunotherapy of alopecia areata with diphencyprone. *Arch Dermatol* 2001; 137: 1063–8.
9. van der Steen PHM, *et al.* Topical immunotherapy for alopecia areata: re-evaluation of 139 cases after an additional follow-up period of 19 months. *Dermatology* 1992; 184: 198–201.

Warts. Diphencyprone has been tried in the treatment of recalcitrant warts. The successful treatment of digital or plantar warts in 42 of 60 patients has been described.[1] The patients were initially sensitised with a 2% topical solution of diphencyprone in acetone, then the warts treated every 1 to 4 weeks with solutions ranging from 0.01 to 6%. In another series,[2] diphencyprone in a paraffin ointment was effective in the clearance of palmar, plantar, palmoplantar, and periungual warts in 135 of 154 patients. A concentration of diphencyprone 2% was used for the initial sensitisation, and concentrations of 0.5 to 4% were used for treatment once every 3 weeks. After initial sensitisation with diphencyprone 2% in acetone, a preparation of diphencyprone with salicylic acid in white soft paraffin applied every night as tolerated was reported to be successful in 44 of 50 patients treated for palmoplantar warts.[3] The concentration of diphencyprone in the ointment ranged from 0.01 to 0.2%, and the concentration of salicylic acid was 15%.

1. Buckley DA, *et al.* Recalcitrant viral warts treated by diphencyprone immunotherapy. *Br J Dermatol* 1999; 141: 292–6.
2. Upitis JA, Krol A. The use of diphenylcyclopropenone in the treatment of recalcitrant warts. *J Cutan Med Surg* 2002; 6: 214–17.
3. Armour K, Orchard D. Treatment of palmoplantar warts with a diphencyprone and salicylic acid ointment. *Australas J Dermatol* 2006; 47: 182–5.

Dipyrithione *(USAN, rINN)*

Bispiriyon; Bispyrithione; Dipiritiona; Dipyrithionum; OMDS; Piriyon Disülfit; Pyrithione Disulfide; Дипиритион.

2,2'-Dithiodipyridine 1,1'-dioxide.

$C_{10}H_8N_2O_2S_2$=252.3

CAS — 3696-28-4.

UNII — 9L87N86R9A.

Profile

Dipyrithione is reported to have antibacterial and antifungal properties and is included in preparations for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Perkapil.

Multi-ingredient Preparations. *Canad.*: Dan-Tar Plus†; Polytar AF; *Switz.*: Crimanex.

Dithiosalicylic Acid

Ditiosalicílico, ácido; Дитиосалициловая Кислота.

2-Hydroxybenzenecarbodithioic acid.

$C_7H_6OS_2$=170.2

CAS — 527-89-9.

UNII — 8LV29H49A3.

Profile

Dithiosalicylic acid has been used in multi-ingredient preparations used topically for the treatment of acne and seborrhoeic dermatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Sacnel.

Dithranol *(BAN, rINN)*

Anthralin; Antralin; Antralina; Dioxlantranol; Dioxyanthranol; Dithranolum; Ditranol; Ditranoli; Ditranolis; Lignolina; Дитранол.

1,8-Dihydroxyanthrone; 1,8-Dihydroxy-9(10*H*)-anthracenone.

$C_{14}H_{10}O_3$=226.2

CAS — 1143-38-0 (dithranol); 16203-97-7 (dithranol triacetate).

ATC — D05AC01.

ATC Vet — QD05AC01.

UNII — U8CJK0JH5M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Dithranol). A yellow or brownish-yellow, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in acetone; soluble in dichloromethane; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Anthralin). A yellowish-brown, odourless, crystalline powder. Insoluble in water; slightly soluble in alcohol, in ether, and in glacial acetic acid; soluble in acetone, in chloroform, in benzene, and in solutions of alkali hydroxides. The filtrate from a suspension in water is neutral to litmus. Store at a temperature of 8 degrees to 15 degrees in airtight containers. Protect from light.

Stability. The stability of dithranol has been studied in several bases and vehicles.[1-4] The weaker preparations of dithranol may be less stable.[1,3,4] Salicylic acid is included in dithranol preparations as an antoxidant and its inclusion in pastes also containing zinc oxide prevents their discoloration due to the inactivation of dithranol by zinc oxide.[5] However, zinc oxide or starch can be omitted from dithranol pastes without loss of efficacy provided stiffness is maintained.[5] Addition of ascorbic or oxalic acid may improve dithranol's stability in *'Unguentum Merck'* but salicylic acid appears to be ineffective.[1] The effect of salicylic acid on the instability of dithranol in yellow soft paraffin is variable[1,2] and its inclusion has been questioned as it can be irritant and percutaneous absorption can be significant.[1] Dithranol is relatively stable in white soft paraffin.[1]

The application of any type of heat and contact with metal spatulas should be avoided during the manufacture of dithranol pastes[6] and if milling facilities are not available dithranol can be incorporated into Lassar's paste by dissolving it first in chloroform.[5]

1. Green PG, *et al.* The stability of dithranol in various bases. *Br J Dermatol* 1985; 113 (suppl 29): 26.
2. Lee RLH. Stability of dithranol (anthralin) in various vehicles. *Aust J Hosp Pharm* 1987; 17: 254–8.
3. Hiller C, *et al.* How stable is dithranol? An investigation into the degradation of different dithranol formulations. *Pharm Pract* 1995; 5: 428–31.
4. Thoma K, Holzmann C. Stabilization of dithranol in topical formulations. *Acta Pharm Hung* 1998; 68: 313–21.
5. Comaish S, *et al.* Factors affecting the clearance of psoriasis with dithranol (anthralin). *Br J Dermatol* 1971; 84: 282–9.
6. *PSGB Lab Report P/79/1* 1979.

Uses and Administration

Dithranol is used in the treatment of subacute and chronic psoriasis, usually in one of two ways.

Conventional treatment is commonly started with an ointment or paste containing 0.1% dithranol (0.05% in very fair patients) applied for a few hours; the strength is gradually increased as necessary to 0.5%, occasionally to 1%, and the duration of contact extended to overnight periods or longer. The preparation is sparingly and accurately applied to the lesions only. If, on initial treatment, lesions spread or excessive irritation occurs, the concentration of dithranol or the frequency of application should be reduced; if necessary, treatment should be stopped. After each treatment period the patient should bathe or shower to remove any residual dithranol.

For *short-contact therapy* dithranol is usually applied in a soft basis to the lesions for up to 60 minutes daily, before being washed off. As with conventional treatment the strength used is gradually increased from 0.1 to 2% but strengths up to 5% have been used. Surrounding unaffected skin may be protected by white soft paraffin.

Treatment for psoriasis should be continued until the skin is entirely clear. Intermittent courses may be needed to maintain the response. Treatment schedules often involve coal tar and UV irradiation (preferably UVB) before the application of dithranol (see below). Salicylic acid is included in many topical preparations of dithranol.

A cream containing dithranol triacetate has been used similarly to dithranol in conventional treatment of psoriasis.

Alopecia. Dithranol cream (0.5 to 1%) applied for 20 to 60 minutes to the scalp and then washed off, has been found to be of benefit in the treatment of alopecia areata (p. 1682.3). However, at least 6 months of treatment may be required for a cosmetically acceptable result.[1] The response rate has, however, been difficult to evaluate because of the small number of reports, and although it has been widely prescribed for limited patchy alopecia areata, some guidelines conclude that there is no convincing evidence of efficacy.[2]

1. Meidan VM, Touitou E. Treatments for androgenetic alopecia and alopecia areata: current options and future prospects. *Drugs* 2001; 61: 53–69.
2. MacDonald Hull SP, *et al.* British Association of Dermatologists. Guidelines for the management of alopecia areata. *Br J Dermatol* 2003; 149: 692–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Alopecia%20Areata.pdf (accessed 20/07/10)

Psoriasis. Dithranol used alone or with coal tar, (with or without ultraviolet light), continues to be one of the drugs of first-line treatment for psoriasis (p. 1688.1). It is particularly suited to the treatment of stable chronic plaque psoriasis but unlike coal tar, is irritant to healthy skin and care is required to ensure that it is only applied to lesions. Treatment with dithranol is therefore more feasible when the plaques are large, or few in number. Use with coal tar may help to reduce the irritant effects of dithranol without affecting efficacy. conventional treatment with dithranol is time consuming and more suitable for use on hospital inpatients. Dithranol formulated in stiff preparations such as Lassar's paste to minimise spreading to perilesional skin is left on overnight covered with a suitable dressing and washed off the next day. Treatment is usually started with a concentration of 0.1% (0.05% in fair-skinned patients) and gradually increased according to the response and irritation produced. Cream formulations may be less effective but are more suitable for domestic use. Short-contact therapy in which concentrations of up to 5% of dithranol are applied daily for up to 1 hour is more suitable for use on an outpatient basis and there appears to be little reduction in efficacy; irritation and staining may also be reduced.

Dithranol is also used with UVB phototherapy and there have been many modifications of the original Ingram's regimen in which dithranol is applied after bathing in a tar bath and exposure to ultraviolet light. Inpatient stays of up to 3 weeks may be required but long periods of remission can be obtained.

Reviews.

1. Mahrle G. Dithranol. *Clin Dermatol* 1997; 15: 723–37.

Adverse Effects and Precautions

Dithranol may cause a burning sensation especially on perilesional skin. Patients with fair skin may be more sensitive than those with dark skin. It is irritant to the eyes and mucous membranes. Use on the face, skin flexures, and genitals should be avoided. Hands should be washed after use.

Dithranol should not be used for acute or pustular psoriasis or on inflamed skin. It stains skin, hair, some fabrics, plastics, and enamel. Staining of bathroom ware may be less of a problem with creams than ointments. Stains on skin and hair slowly disappear on cessation of treatment.

Handling. Dithranol is a powerful irritant and should be kept away from the eyes and tender parts of the skin.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dithranol as possibly porphyrinogenic: it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Micanol; *Canad.*: Anthraforte; Anthranol; Anthrascalp; *Ger.*: Micanol; *India*: Psorinol†; *Indon.*: Anthramed; *Irl.*: Dithrocream; *Israel*: Dithrocream; Micanol†; *Ital.*: Psoriderm†; *NZ*: Micanol; *Port.*: Micanol; *S.Afr.*: Anthranol†; *Singapore*: Micanol; *Spain*: Micanol; *UK*: Dithrocream; Micanol; *USA*: Dritho-Scalp; Psoriatec; Zithranol-RR.

Multi-ingredient Preparations. *Austral.*: Dithrasal†; *Fr.*: Anaxeryl; *Ger.*: Psoradexan; Psoralon MT; *Gr.*: Filorose; *Hong Kong*: Dithrasal†; *India*: Derobin-HC; Derobin; *Singapore*: Dithrasal; *Spain*: Lapices Epiderm Metadier†; *Turk.*: Psoraks; *UK*: Psorin; Psorin.

Pharmacopoeial Preparations
BP 2014: Dithranol and Salicylic Acid Ointment; Dithranol Cream; Dithranol Ointment; Dithranol Paste;
USP 36: Anthralin Cream; Anthralin Ointment.

Drometrizole *(USAN, rINN)*

Drometrizol; Drométrizol; Drometrizolum; Дрометризол.
2-(2*H*-Benzotriazol-2-yl)-*p*-cresol.
$C_{13}H_{11}N_3O$=225.3
CAS — 2440-22-4.
UNII — 5X93W9OFZL.

Drometrizole Trisiloxane

Дрометризола Трисилоксан.
2-(2*H*-Benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-[1,3,3,3-tetramethyl-1-[(trimethylsilyl)oxy]-1-disiloxanyl]propyl)phenol.
$C_{24}H_{39}N_3O_3Si_3$=501.8
CAS — 155633-54-8.

NOTE. Mexoryl XL and Silatrizole are trade names that have been used for drometrizole trisiloxane.

Profile

Drometrizole trisiloxane is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Anthelios; Antherpos; Cetaphil UV Defense; *Braz.*: Anthelios Helioblock Dermopediatrics; Anthelios Helioblock Spray; Anthelios Helioblock W40; Anthelios Helioblock; Antherpos; Helioblock†; Helioblock; Melani-D Maos; *Canad.*: Anthelios XL; Anthelios XL; Anthelios; Antherpos†; Aqualia; Creme Visage; Face Multi-Protection; Face Multi-Protection; High Protection Cream; Lait Protecteur; Lip Protection; Ombrelle Cream; Ombrelle Kids; Ombrelle Stick; Rosaliac Sun Protection; Sunscreen Cream; Ultra Protection Sunscreen; Ultra-Fluid Body Milk; Ultra-Fluid Sun Protection; *Chile*: Anthelios AC; Anthelios AE; Anthelios Dermo-Pediatrics; Anthelios Extremo; Anthelios Spray; Anthelios W; Anthelios XL; Anthelios XL; Cetaphil Defense; Hydraphase XL; Melani-D; Redermic XL; *Fr.*: Anthelios; Anthelios; Anthelios; Antherpos†; Capital Soleil; *Irl.*: Anthelios†; *Malaysia*: Cetaphil UVA/UVB Defense; *Singapore*: Anthelios XL Extreme; Cetaphil UVA/UVB; *UK*: Anthelios XL.

Ecamsule *(USAN, rINN)*

Ecamsul; Ecamsule; Ecamsulum; Экамсул.
(±)-(3*E*,3′*E*)-3,3′-(*p*-Phenylenedimethylidyne)bis(2-oxo-10-bornanesulfonic acid); Terephthalylidene-3,3′-dicamphor-10,10′-disulfonic acid.
$C_{28}H_{34}O_8S_2$=562.7
CAS — 92761-26-7.
UNII — M94R1PM439.

NOTE. Mexoryl SX is a trade name that has been used for ecamsule.

Pharmacopoeias. *US* includes a solution.

USP 36: (Ecamsule Solution). An aqueous solution containing 30 to 34% w/w of ecamsule. Store in airtight containers. Protect from light.

Profile

Ecamsule, a camphorsulfonic acid derivative, is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Anthelios; Antherpos; Cetaphil UV Defense; *Braz.*: Anthelios Helioblock Dermopediatrics; Anthelios Helioblock Spray; Anthelios Helioblock W30; Anthelios Helioblock W40; Anthelios Helioblock; Antherpos; Helioblock; Melani-D Maos; *Canad.*: Anthelios XL; Anthelios†; Anthelios; Aqualia; Baume Levres; Biotherm†; Creme Fondante†; Creme Visage; Face Multi-Protection; Face Multi-Protection; High Protection Cream; Hydraphase UV; Lait Ecran Enfants†; Lait Protecteur; Lotion Tres Douce; Lotion Vapo†; Multi Recharge; Ombrelle Cream; Ombrelle Kids; Ombrelle L'Oreal Suncare Research Kids; Ombrelle Lotion Extreme; Ombrelle Lotion; Ombrelle Lotion; Ombrelle Lotion; Ombrelle Sport Lotion; Protective Gel†; Rosaliac Sun Protection; Sunscreen Cream; Thermal FIX UV†; Ultra-Fluid Body Milk; Ultra-Fluid Protection†; Ultra-Fluid Sun Protection; *Chile*: Anthelios AC; Anthelios AE; Anthelios Dermo-Pediatrics; Anthelios Extremo; Anthelios Spray; Anthelios W; Anthelios XL; Cetaphil Defense; Hydraphase XL; Redermic XL; *Fr.*: Anthelios; Anthelios; Anthelios; Antherpos†; Capital Soleil; *Irl.*: Anthelios†; *Malaysia*: Cetaphil UVA/UVB Defense; *Singapore*: Anthelios XL Extreme; Cetaphil UVA/UVB; *UK*: Ambre Solaire; Anthelios XL; *USA*: Anthelios 40; Anthelios SX; Capital Soleil; UV Protective.

Efalizumab *(USAN, rINN)*

Anti-CD11a; Efalizumab; Efalizumabum; Hu-1124; Эфализумаб.
Immunoglobulin G1, anti-(human antigen CD11a)(human-mouse monoclonal hu1124 γ1-chain), disulfide with human-mouse monoclonal hu1124 light chain, dimer.
CAS — 214745-43-4.
ATC — L04AA21.
ATC Vet — QL04AA21.
UNII — XX2MN88N5D.

Uses and Administration

Efalizumab is a humanised monoclonal antibody that binds to human CD11a on leucocytes to inhibit the activation of T-lymphocytes. It has been used for the treatment of chronic moderate to severe plaque psoriasis (p. 1688.1) in patients aged 18 years and over. Efalizumab is given by subcutaneous injection. The initial dose is 700 micrograms/kg, followed by a weekly dose of 1 mg/kg; a single dose should not exceed 200 mg. Treatment is given for 12 weeks, then continued in those who have responded. However, in early 2009 both the FDA and the EMEA reviewed the safety of efalizumab, in response to case reports of progressive multifocal leukoencephalopathy, and the drug was subsequently withdrawn from many markets including Australia, Canada, the USA, and Europe.

References.

1. Lebwohl M, *et al.* A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. *N Engl J Med* 2003; 349: 2004–13.
2. Gordon KB, *et al.* Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. *JAMA* 2003; 290: 3073–80. Correction. *ibid.* 2004; 291: 1070.
3. Menter A, *et al.* Efficacy and safety observed during 24 weeks of efalizumab therapy in patients with moderate to severe plaque psoriasis. *Arch Dermatol* 2005; 141: 31–8.
4. Leonardi CL, *et al.* Extended efalizumab therapy improves chronic plaque psoriasis: results from a randomized phase III trial. *J Am Acad Dermatol* 2005; 52: 425–33.
5. Wellington K, Perry CM. Efalizumab. *Am J Clin Dermatol* 2005; 6: 113–20.
6. Jordan JK. Efalizumab for the treatment of moderate to severe plaque psoriasis. *Ann Pharmacother* 2005; 39: 1476–82.
7. Menter A, *et al.* Long-term management of plaque psoriasis with continuous efalizumab therapy. *J Am Acad Dermatol* 2006; 54 (suppl 1): S182–S188.
8. Duberteret L, *et al.* Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. *Br J Dermatol* 2006; 155: 170–81.
9. Leonardi C, *et al.* Efalizumab: results of a 3-year continuous dosing study for the long-term control of psoriasis. *Br J Dermatol* 2008; 158: 1107–16.

Adverse Effects and Precautions

The most common adverse affects associated with efalizumab are flu-like symptoms including chills, fever, headache, myalgia, and nausea. These reactions are dose-related in both incidence and severity and usually occur within two days after the first two injections. Other adverse effects include acne, back pain, and elevations in alkaline phosphatase concentrations and liver function values. More serious adverse effects of efalizumab include arthritis, interstitial pneumonitis, hypersensitivity reactions, inflammatory polyradiculoneuropathy, and thrombocytopenia. Treatment should be stopped in patients who develop such reactions. Other neurological adverse events have included facial palsy and transverse myelitis. Severe haemolytic anaemia, diagnosed 4 to 6 months after the start of efalizumab treatment, has been reported. Treatment should be stopped immediately if haemolytic anaemia occurs. Asymptomatic leucocytosis or lymphocytosis commonly occurs during treatment. Worsening of psoriasis or development of variant forms (pustular, erythrodermic, or guttate) have been reported during and after stopping efalizumab therapy.

As a result of immunosuppression, patients given efalizumab are at increased risk of infection. It should not be given to patients with a serious infection and should be used with care in those with chronic infection or a history of recurring infection. Serious bacterial, viral, fungal, and other opportunistic infections have occurred. Reports of progressive multifocal leukoencephalopathy associated with JC virus infection have prompted the withdrawal of efalizumab from many markets (see Effects on the Nervous System, p. 1703.1). Live and live-attenuated vaccines should not be given during efalizumab treatment because of the risk of infection; response to all vaccines may also be reduced. Efalizumab should be withheld from 8 weeks before until 2 weeks after vaccination. Immunosuppression caused by efalizumab might also increase the risk of developing malignancies, so it should be used with care or avoided in patients with a history, or at high risk, of malignancy. Based on studies in *mice*, efalizumab is not recommended for use in children because of the potential risk of permanent suppression of humoral immunity with repeated administration.

Assessment of the platelet count is advised before starting therapy and monthly during early treatment. Prequency of monitoring may be decreased with ongoing treatment.

Incidence of adverse effects. The safety data from 13 controlled and open-label studies of efalizumab in psoriasis have been analysed.[1] During the first 12 weeks of therapy the most common events in patients treated with efalizumab were headache, fever, chills, nausea, vomiting, or myalgia, starting within 48 hours of dosing. In 4 controlled studies that included 1620 patients treated with efalizumab and 715 with placebo, about a third of efalizumab-treated patients reported headache, while chills, nausea, and pain occurred in around 10%, and fever and myalgia in about 8%. These events usually occurred with the first 1 or 2 doses of efalizumab but by the third and subsequent doses the incidence was similar to that in the placebo group. Atypical or unusual worsening of psoriasis and the development of variant forms, particularly guttate psoriasis, were reported in 3.2% of patients treated with efalizumab; other forms included psoriatic erythroderma, inverse psoriasis, palmoplantar psoriasis, and pustular psoriasis. In 5 studies of extended therapy for 13 to 60 weeks (1115 patients treated for 13 to 24 weeks and 228 for 60 weeks) the rate of adverse effects remained low, there was no new pattern of serious adverse effects, and there was no evidence of cumulative toxicity. An analysis of infection risk found similar rates of mild to moderate and serious infections in patients treated with either efalizumab or placebo. Nevertheless, efalizumab should not be used in patients with pre-existing serious infection. Anti-efalizumab antibodies were found in 67 of 1063 patients, but there was no apparent effect on efficacy, safety, or pharmacodynamics.

There have been infrequent reports of new onset or recurrent severe arthritis, including psoriatic arthritis, in patients treated with efalizumab. Separate analyses[1,2] of pooled study data both found that the incidence of arthropathy events was low (less than 4%) and similar for patients treated with either efalizumab or placebo. However, there was some suggestion[2] that patients with a history of arthropathy and those who have a poor clinical response to efalizumab may be at higher risk.

1. Papp KA, *et al.* Safety of efalizumab in patients with moderate to severe chronic plaque psoriasis: review of clinical data. *J Cutan Med Surg* 2005; 9: 313–23.
2. Pinceli C, *et al.* The incidence of arthropathy adverse events in efalizumab-treated patients is low and similar to placebo and does not increase with long-term treatment: pooled analysis of data from phase III clinical trials of efalizumab. *Arch Dermatol Res* 2006; 298: 329–38.

Carcinogenicity. Efalizumab is an immunosuppressant and as such might increase the risk of malignancy. An analysis[1] of pooled data from clinical studies that included 2980 patients given efalizumab found 51 patients (1.7%) with 67 malignancies. Most cases were of non-melanoma skin cancer (51 cases in 35 patients) and it was found that many had risk factors for skin cancer. Other cases included 3 lymphomas, 12 solid tumours at various sites, and 1 malignant melanoma. However, when compared with patients given placebo and data from 2 external cohorts of psoriasis patients (to allow for the increased risk of skin cancers seen in psoriasis patients compared with the general population) there was no evidence that efalizumab increased the risk of developing a malignancy. Nevertheless, further data are needed to determine whether efalizumab has any long-term effect on the development of malignancies.

1. Leonardi CL, *et al.* A review of malignancies observed during efalizumab (Raptiva) clinical trials for plaque psoriasis. *Dermatology* 2006; 213: 204–14.

Effects on the blood. *Thrombocytopenia* has been described in 6 patients given efalizumab.[1] In 5 cases it started 8 to 12 weeks after starting weekly efalizumab. In all cases the platelet counts recovered quickly after efalizumab was stopped; in 5 cases corticosteroids were also given. In another case a woman presented with *pancytopenia* 4 weeks after starting efalizumab therapy.[2] Efalizumab was stopped and the patient treated with granulocyte colony-stimulating factor, normal immunoglobulin, oral prednisone, platelet transfusion, and darbepoetin alfa. Cell counts returned to normal limits within 4 weeks. Asymptomatic *thrombotic thrombocytopenic purpura* was diagnosed after 6 weeks of efalizumab therapy in a woman with psoriasis; the reaction was successfully managed with plasma exchange.[3]

1. Warkentin TE, Kwon P. Immune thrombocytopenia associated with efalizumab therapy for psoriasis. *Ann Intern Med* 2005; 143: 761–3.

2. Tom WL, *et al.* Efalizumab-induced autoimmune pancytopenia. *Br J Dermatol* 2006; 155: 1045–7.
3. Thachil J, Martlew V. Thrombotic thrombocytopenic purpura with the use of efalizumab for psoriasis. *Br J Dermatol* 2008; 158: 1138–9.

Effects on the nervous system. In early 2009, efalizumab was withdrawn from the market in the USA[1] and Europe[2] after reports of progressive multifocal leukoencephalopathy; some of the cases were fatal. This rare neurological condition, caused by JC virus infection, had occurred in a small number of patients who had been using efalizumab for more than 3 years in the treatment of moderate to severe plaque psoriasis. (Efalizumab has since been withdrawn from other countries including Australia and Canada.)

Aseptic meningitis has been reported with efalizumab. Severe headache developed 48 hours after the first dose of efalizumab in 2 cases, which was followed after 12 to 24 hours by neck stiffness.[3,4] One of the patients also had photophobia and phonophobia.[3]

1. FDA. FDA statement on the voluntary withdrawal of Raptiva from the U.S. market (issued 8th April, 2009). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm143347.htm (accessed 22/07/10)
2. EMEA. Public statement on Raptiva (efalizumab): withdrawal of the marketing authorisation in the European Union (issued 3rd August, 2009). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2009/11/news_detail_000060.jsp&mid=WC0b01ac058004d5c1&murl=menus/news_and_events/news_and_events.jsp&jsenabled=true (accessed 22/07/10)
3. Kluger N, *et al.* Efalizumab-induced aseptic meningitis. *Br J Dermatol* 2007; 156: 189–91.
4. Rivas-Rodríguez R, *et al.* Efalizumab-induced aseptic meningitis. *Farm Hosp* 2007; 31: 70–1.

Interactions

For a warning concerning the use of live vaccines in patients receiving efalizumab see Adverse Effects and Precautions, p. 1702.2.

Pharmacokinetics

Peak plasma concentrations of efalizumab occur about 1 to 2 days after subcutaneous injection, with a bioavailability of about 50%. Steady state is reached at week 4 of weekly dosing. Efalizumab is metabolised by intracellular degradation. It is cleared by non-linear saturable elimination and the time to elimination after the last dose is about 25 days.

References.
1. Mortensen DL, *et al.* Pharmacokinetics and pharmacodynamics of multiple weekly subcutaneous efalizumab doses in patients with plaque psoriasis. *J Clin Pharmacol* 2005; 45: 286–98.
2. Sun Y-N, *et al.* Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. *J Clin Pharmacol* 2005; 45: 468–76.
3. Joshi A, *et al.* An overview of the pharmacokinetics and pharmacodynamics of efalizumab: a monoclonal antibody approved for use in psoriasis. *J Clin Pharmacol* 2006; 46: 10–20.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Raptiva; *Austral.*: Raptiva†; *Austria*: Raptiva†; *Braz.*: Raptiva†; *Canad.*: Raptiva†; *Cz.*: Raptiva†; *Denm.*: Raptiva†; *Fin.*: Raptiva†; *Fr.*: Raptiva†; *Ger.*: Raptiva†; *Gr.*: Raptiva†; *Hong Kong*: Raptiva†; *Irl.*: Raptiva†; *Israel*: Raptiva; *Ital.*: Raptiva†; *Malaysia*: Raptiva†; *Mex.*: Raptiva†; *Neth.*: Raptiva†; *Norw.*: Raptiva†; *NZ*: Raptiva; *Port.*: Raptiva†; *Rus.*: Raptiva (Раптива); *Singapore*: Raptiva†; *Spain*: Raptiva†; *Swed.*: Raptiva†; *Switz.*: Raptiva†; *Turk.*: Raptiva; *UK*: Raptiva†; *USA*: Raptiva†.

Ensulizole *(USAN, rINN)*

Ensulizol; Ensulizolum; Phenylbenzimidazole Sulphonic Acid; Энсулизол.
2-Phenyl-1*H*-benzimidazole-5-sulphonic acid.
$C_{13}H_{10}N_2O_3S$=274.3
CAS — 27503-81-7.
UNII — 9YQ9DI1W42.

NOTE. Eusolex 232 and Neo-Heliopan Hydro are trade names that have been used for ensulizole.

Pharmacopoeias. In *US.*

USP 36: (Ensulizole). A white to ivory-coloured, odourless powder. Practically insoluble in water and in oily solvents; soluble in alcohol; its salts are freely soluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Ensulizole is used topically as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Coppertone Tan Magnifier; Hawaiian Tropic Dark Tanning.

Multi-ingredient Preparations. *Arg.*: Fotocrem 50; Fotocrem 50; Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Ultra; Leico P Ultra; Leico Ultrablock Extreme; Leico Ultrablock†; Ozonosol; Ozonosol; Refrane Total; *Austral.*: Sunsense Sport; *Braz.*: Isotrexol; Neutrogena Healthy Skin Anti-rugas com FPS 15; Sunmax Acqua; *Canad.*: Anti-Aging Moisturizing†; Aqua Fusion†; Aqua Soleil; Aqua Soleil; Bienfait Multi-vital†; Creme Haute Exigence; Creme Solaire Tres Haute Protection Special Intolerances; Creme Solaire Tres Haute Protection Special Peaux Sensibles; Dermaglow†; Dove Face†; Fluide Hydratant Quotidien; Future B; High Resolution†; Hydra-C; Hydrafresh; Kids Sunscreen; Lotion Sport; Marcelle Essentials; Marcelle Multi-Defense; Mesoestetic; Mesoestetic; Moisture Rescue; Multi Recharge; Neutrogena Anti-Wrinkle; Neutrogena Day Moisture; Neutrogena Healthy Defense†; Nivea Visage Q10 Advanced Wrinkle Reducer†; Nutritionist Regenerating Moisturizer†; Oil of Olay Total Effects†; Ombrelle Lotion; Ombrelle Lotion; Premium Sunscreen; Primordiale; Protective Gel†; Refinish†; Renergie Microlift RARE†; Renergie Microlift†; Revitalizing Q10 Moisturizer†; Shiseido Skincare Day Moisture Protection; Skin Clarifying; Skin Renew; Sun Defense; Sunscreen Lotion Ecran; Triple Protect; Ultra Protection Sunscreen; Ultra-Lift Anti-Wrinkle†; Vita Lift; *Chile*: Emolan Bloqueador Solar; Eucerin Q10 Active; Eucerin Solar†; Eucerin; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotoprotector Isdin-25 Pediatrics†; Hidrafil†; Neutrogena Crema Humectante; Neutrogena Healthy Defense; Neutrogena Healthy Skin; Nutraisdin; *Fr.*: Trio S; *Hong Kong*: Sunsense Ultra; *India*: Nuface; *Malaysia*: Sunsense Ultra; *Mex.*: Filtrosol; Hidrafil; *Neth.*: Contralum Ultra; *Singapore*: Sunsense Ultra; *Thai.*: Eucerin Sun Sensitive Skin†; *USA*: Durascreen; Eucerin Dry Skin Care Daily Facial; Eucerin Moisturizing Face; Hawaiian Tropic Protective Tanning Dry; Neutrogena Intensified; Nivea Sun; Oil of Olay; *Venez.*: Filtrosol.

Enzacamene *(USAN, rINN)*

Enzacamène; Enzacameno; Enzacamenum; Methyl Benzylidene Camphor; 3-(4-Methylbenzylidene)borman-2-one; 3-(4-Methylbenzylidene)camphor; Энзакамен.
1,7,7-Trimethyl-3-[(4-methylphenyl)methylene]bicyclo[2.2.1]heptan-2-one.
$C_{18}H_{22}O$=254.4
CAS — 36861-47-9 (DL-form); 38102-62-4 (form unspecified).
UNII — 8I3XWY40L9.

NOTE. Eusolex 6300, Neo-Heliopan MBC, and Parsol 5000 are trade names that have been used for enzacamene.

Pharmacopoeias. In *US.*

USP 36: (Enzacamene). A white, fine crystalline powder. M. p. between 66 degrees and 68 degrees. Practically insoluble in water; freely soluble in alcohol; very soluble in chloroform. Store in airtight containers.

Profile

Enzacamene is a camphor derivative used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Clear Zinke; *NZ*: Hamilton Sunscreen†.

Multi-ingredient Preparations. *Arg.*: Fotoprotector Extrem Pediatrics; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Extrem; Fotoprotector Ultra; Fotoprotector; Fotoprotector; Ureadin Facial; *Austral.*: Hamilton Family Sunscreen; Hamilton Family Sunscreen; Hamilton Family Sunscreen; Hamilton Optimal; Hamilton Quadblock; Hamilton Quadblock; Hamilton Solastick; Hamilton Sportblock Broad Spectrum Milk†; Hamilton Toddler; Le Tan Sunscreen Lotion†; Lip-Eze; Sunsense Sport; Sunsense Sport; Sunsense Ultra; Sunsense; Sunsense; Superfade UV Hand Shield; UV Triplegard Kids; UV Triplegard Sports; Zinc Cream White; *Braz.*: Fotoprotetor Isdin Extrem Infantil†; Fotoprotetor Isdin Extrem UVA†; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Extrem; Fotoprotetor Isdin Infantil†; Fotoprotetor Isdin†; Fotoprotetor Spray Isdin†; Sunmax 30; Sunmax Acqua; Uviess; *Canad.*: Antheliос†; Biotherm†; Lotion Sport; Mesoestetic Rejuva; ROC Minesol Protect Ultra High; ROC Minesol Protect Very High†; Soleil Protexion Velvet Moisture; Soleil Protexion Velvet Moisture; Sunscreen Lotion Ecran; *Chile*: Emolan Bloqueador Solar; Emolan Gel Protector Solar; Emolan†; Eucerin Solar†; Fotoprotector Isdin Dry Oil†; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem Plus†; Fotoprotector Isdin Extrem†; Fotoprotector Isdin Extrem; Fotoprotector Isdin Extrem; Fotoprotector Isdin F-15†; Fotoprotector Isdin Ultra 65†; Fotoprotector Isdin Ultra 90†; Fotoprotector Isdin-25 Pediatrics†; Fotoprotector Isdin-50†; Photoderm AR†; Photoderm Max†; Photoderm Spot†; ROC Minesol Actif; ROC Minesol Protect; ROC Minesol Protect; *Fr.*: SVR 100†; *Hong Kong*: Spectraban 60; Sunsense Clear Mist†; Sunsense Milk Mist†; Sunsense Sport; Sunsense Ultra; Sunsense†; *Indon.*: Intersun; Paranox†; *Irl.*: Antherpos†; *Ital.*: Photoderm Max; *Malaysia*: Spectraban; Sunsense Clear Mist†; Sunsense Milk Mist†; Sunsense Sport Gel†; Sunsense Ultra; *Mex.*: Eclipsol Hydro; Extreme Sun; Heliocare; ProZone Ultra Fluido; ProZone Ultra; Umbrella Plus; Umbrella; *Neth.*: Contralum Ultra; *NZ*: Hamilton Optimal; Hamilton Quadblock; Hamilton Quadblock; Hamilton Solastick; Hamilton Sunscreen; Hamilton Sunscreen; Hamilton Sunscreen; Hamilton Toddler; *Singapore*: Spectraban 60; Sunsense Clear†; Sunsense Milk†; Sunsense Ultra; *Switz.*: Kell-med; *Thai.*: Eucerin Sun Sensitive Skin†; Sebamed Suncream 20; Sebamed Sunlotion 20†; Spectraban†; *UK*: Ambre Solaire; E45 Sun†; *Venez.*: Filtrosol; Photoderm Max.

Erythrulose

DL-Glycero-tetrulose; Эритрулаза.
1,3,4-Trihydroxy-2-butanone.
$C_4H_8O_4$=120.1
CAS — 40031-31-0 (DL-erythrulose); 496-55-9 (D-erythrulose); 533-50-6 (L-erythrulose).

Profile

Application to the skin of preparations containing L-erythrulose slowly produces a brown coloration similar to that caused by exposure to the sun, probably due to a reaction with the amino acids of the skin. It is often used with dihydroxyacetone (p. 1700.1) in artificial suntan preparations. Recommended concentrations are usually 1 to 3% when used with dihydroxyacetone; concentrations of up to 5% have been applied when used alone.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Sunsense Self Tanning System Self Tan; *Braz.*: Sunmax Autobronzeador; *Fr.*: Viticolor; *UK*: VITicolor.

Etretinate *(BAN, USAN, rINN)*

Etretinaatti; Etretinat; Étrétinate; Etretinato; Etretinatum; Ro-10-9359; Этретинат.
Ethyl 3-methoxy-15-apo-β-caroten-15-oate; Ethyl (*all-trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate.
$C_{23}H_{30}O_3$=354.5
CAS — 54350-48-0.
ATC — D05BB01.
ATC Vet — QD05BB01.
UNII — 65M2UDR9AG.

Uses and Administration

Etretinate is a retinoid and is a derivative of tretinoin (p. 1725.2). It has been given orally for the treatment of severe, extensive psoriasis that has not responded to other treatment, especially generalised and palmo-plantar pustular psoriasis. It has also been used in severe congenital ichthyosis, severe Darier's disease (keratosis follicularis) as well as other disorders of keratinisation, and oral lichen planus. Acitretin (p. 1690.3) is now preferred to etretinate.

Therapy is generally started at doses of 0.75 to 1 mg/kg daily in divided oral doses. A maximum dose of 1.5 mg/kg daily should not be exceeded (some licensed product information has suggested a maximum of 75 mg daily). Erythrodermic psoriasis may respond to lower initial doses of 250 micrograms/kg daily, increased at weekly intervals by 250 micrograms/kg daily until optimal response occurs. After the initial response, generally after 8 to 16 weeks of therapy, maintenance doses of 500 to 750 micrograms/kg daily have been given. Therapy should be stopped once lesions have sufficiently resolved.

References.
1. Magis NLJ, *et al.* The treatment of psoriasis with etretinate and acitretin: a follow up of actual use. *Eur J Dermatol* 2000; 10: 517–21.
2. Katugampola RP, Finlay AY. Oral retinoid therapy for disorders of keratinization: single-centre retrospective 25 years' experience on 23 patients. *Br J Dermatol* 2006; 154: 267–76.

Adverse Effects and Precautions

As for Isotretinoin, p. 1707.2 and p. 1709.2.

Donation of blood should be avoided for at least 2 years after cessation of treatment. The period of time during which pregnancy must be avoided after stopping treatment has not been determined; detectable plasma-etretinate concentrations have been reported nearly 3 years after the last dose.

In addition to the references cited below, further references to the adverse effects of etretinate can be found in Isotretinoin, under Effects on the Blood (p. 1707.3), Cardiovascular System (p. 1707.3), Eyes (p. 1707.3), Liver (p. 1708.1), Musculoskeletal System (p. 1708.2), Serum Lipids (p. 1708.3), and the Skin (p. 1709.1), as well as under Vasculitic Syndromes (p. 1709.2).

Carcinogenicity. A report of 2 patients who developed lymphomas while receiving etretinate[1] prompted a report of 3 other malignancies in patients taking etretinate.[2]

1. Woll PJ, *et al.* Lymphoma in patients taking etretinate. *Lancet* 1987; ii: 563–4.
2. Harrison PV. Retinoids and malignancy. *Lancet* 1987; ii: 801.

Effects on the kidneys. Rare cases of impaired renal function associated with etretinate have been described.[1,2] In one report[1] it was also noted that in manufacturer-sponsored studies the mean serum-creatinine concentration had been raised in patients receiving etretinate.

1. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; ii: 1093.
2. Cribier B, *et al.* Renal impairment probably induced by etretinate. *Dermatology* 1992; 185: 266–8.

Oedema. A report of generalised oedema after treatment with etretinate.[1] Five other cases had been reported in the literature and rechallenge in 4 patients had provoked a recurrence. Generalised oedema as part of the capillary leak syndrome has been reported with acitretin (p. 1691.2).

1. Allan S, Christmas T. Severe edema associated with etretinate. *J Am Acad Dermatol* 1988; 19: 140.

Pregnancy. For further information on the teratogenicity of etretinate, see under Acitretin, p. 1691.3.

Interactions

As for Isotretinoin, p. 1710.1.

Anticoagulants. Etretinate has been reported to reduce the therapeutic efficacy of *warfarin* (see Dermatological Drugs, p. 1533.3).

Antiepileptics. Etretinate was ineffective and none of its characteristic mucocutaneous adverse effects occurred in a patient with pityriasis rubra pilaris who was already taking *carbamazepine* and *valproate* for epilepsy. However, there was a clinical response after the carbamazepine had been withdrawn, suggesting that it may have reduced the bioavailability or increased the metabolism of etretinate.[1]

1. Mohammed KN. Unresponsiveness to etretinate during anticonvulsant therapy. *Dermatology* 1992; 185: 79.

Antineoplastics. The risk of developing hepatotoxicity may be increased when etretinate is used with *methotrexate* (see Retinoids, p. 828.3).

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Pharmacokinetics

The mean bioavailability of etretinate is about 40% after oral doses but there is a large interindividual variation. Absorption can be increased if taken with milk or fatty food. Etretinate undergoes significant first-pass metabolism and plasma concentrations of the active carboxylic acid metabolite, acitretin (p. 1690.3), may be detected before those of the parent drug; acitretin may itself be metabolised to etretinate (see p. 1691.3). Both etretinate and acitretin are extensively bound to plasma protein. Etretinate appears to accumulate in adipose tissue after repeated dosing and has a prolonged elimination half-life of about 120 days; detectable serum concentrations have been noted up to 3 years after stopping therapy. Up to 75% of a dose is excreted in the faeces mainly as unchanged drug. Etretinate is also excreted in the urine as metabolites. Etretinate crosses the placenta. Although it is unknown whether etretinate is distributed into breast milk, this would be expected because of its lipophilicity; acitretin, a metabolite of etretinate, has been found in breast milk when it was given to a lactating woman (see Breast Feeding, p. 1691.2).

References.

1. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; 10: 38–62.
2. DiGiovanna JJ, *et al.* Etretinate: persistent serum levels after long-term therapy. *Arch Dermatol* 1989; 125: 246–51.
3. Larsen FG. Pharmacokinetics of etretinate and acitretin with special reference to treatment of psoriasis. *Acta Derm Venereol (Stockh)* 1994; 190 (suppl): 1–33.
4. Wiegand UW, Chou RC. Pharmacokinetics of acitretin and etretinate. *J Am Acad Dermatol* 1998; 39 (suppl): S25–S33.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Tigason.

Fumaric Acid

Ácido alomaleico; Ácido boleico; Acidum Fumaricum; Allomalenic Acid; Boletic Acid; E297; Fumárico, ácido; Kwas fumarowy; Фумаровая Кислота.

trans-Butenedioic acid.

$C_2H_2(CO_2H)_2$=116.1

CAS — 110-17-8.

ATC — D05AX01.

ATC Vet — QD05AX01.

UNII — 88XHZ13131.

Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 31: (Fumaric Acid). White, odourless granules or crystalline powder. Slightly soluble in water and in ether; soluble in alcohol; very slightly soluble in chloroform.

Dimethyl Fumarate *(USAN)*

AZL-O-211089; BG-12; Dimethylfumarate; FAG-201.

Dimethyl (2*E*)-but-2-enedioate.

$C_6H_8O_4$=144.1

CAS — 624-49-7.

UNII — FO2303MNI2.

Uses and Administration

Fumaric acid and some of its derivatives have been used in the treatment of psoriasis and other skin disorders (see below).

Dimethyl fumarate is used in the treatment of relapsing forms of multiple sclerosis (see below). A modified-release preparation is given orally in an initial dose of 120 mg twice daily. After 7 days this should be increased to a maintenance dose of 240 mg twice daily.

Fumaric acid is also used as an acidifier and flavouring agent in foods.

Multiple sclerosis. Dimethyl fumarate, mainly via its active metabolite monomethyl fumarate, is reported to activate the nuclear factor (erythroid-derived 2)-like (Nrf2) pathway involved in cellular response to oxidative stress, and the potential immunomodulatory and neuroprotective effects of dimethyl fumarate have been studied in multiple sclerosis (p. 996.3). Compared with placebo, it has reduced relapse rates and improved some other outcome measures in patients with relapsing-remitting disease.[1,2]

1. Fox RJ, *et al.* CONFIRM Study Investigators. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med* 2012; 367: 1087–97. Correction. *ibid.*; 1673.
2. Gold R, *et al.* DEFINE Study Investigators. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med* 2012; 367: 1098–1107.

Skin disorders. Fumaric acid, its sodium salts, and derivatives such as dimethyl fumarate, monoethyl fumarate (ethyl hydrogen fumarate), and octil hydrogen fumarate have been used, both topically and systemically, in the treatment of psoriasis (p. 1688.1) and other skin disorders. Dimethyl fumarate appears to be the most active compound given orally but combination with various salts of monoethyl fumarate has been claimed to improve efficacy.[1–6] However, there have been reports of acute renal failure associated with treatment and the German Federal Office of Health has expressed the opinion that the available evidence did not establish the value of fumaric acid derivatives in psoriasis or other skin disorders.[7] A subsequent retrospective analysis of 41 patients who received fumaric acid esters orally, for between 1 and 14 years, suggested that these drugs might be effective,[8] and a later review suggested that they may be of value in refractory psoriasis.[9]

1. van Loenen AC, *et al.* Fumaarzuurtherapie: van fictie tot werkelijkheid? *Pharm Weekbl* 1989; 124: 894–900.
2. Kolbach DN, Nieboer C. Fumaric acid therapy in psoriasis: a long-term retrospective study on the effect of fumaric acid combination (FAC-BC) therapy and dimethyl-fumaric acid ester (DMFAE) monotherapy. *Br J Dermatol* 1990; 123: 534–5.
3. Nugteren-Huying WM, *et al.* Fumaric acid therapy for psoriasis: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol* 1990; 22: 311–12.
4. Altmeyer PJ, *et al.* Antipsoriatic effect of fumaric acid derivatives: results of a multicenter double-blind study in 100 patients. *J Am Acad Dermatol* 1994; 30: 977–81.
5. Mrowietz U, *et al.* Treatment of severe psoriasis with fumaric acid esters: scientific background and guidelines for therapeutic use. *Br J Dermatol* 1999; 141: 424–9.
6. Ständer H, *et al.* Efficacy of fumaric acid ester monotherapy in psoriasis pustulosa palmoplantaris. *Br J Dermatol* 2003; 149: 220–2.
7. Anonymous. Fumaric acid derivatives and nephrotoxicity. *WHO Drug Inf* 1990; 4: 28.
8. Hoefnagel JJ, *et al.* Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; 149: 363–9.
9. Harries MJ, *et al.* Fumaric acid esters for severe psoriasis: a retrospective review of 58 cases. *Br J Dermatol* 2005; 153: 549–51.

Adverse Effects and Precautions

Adverse effects of dimethyl fumarate and other fumaric acid derivatives include gastrointestinal disturbances, abdominal pain, raised hepatic transaminases, and skin reactions such as rash and pruritus. Flushing is common but may be reduced by giving the fumarate with food. The effect generally starts soon after beginning therapy and improves or resolves over time.

Lymphopenia commonly occurs in patients given fumarates. A complete blood count should be taken before starting and then annually during therapy. Transient eosinophilia has also been reported.

There have been reports of acute renal failure associated with fumarates (see Skin Disorders, above).

Reported adverse effects[1] with fumaric acid derivatives were generally mild in a retrospective study of 66 patients with psoriasis, with only 1 case of elevated serum creatinine; however, lymphocytopenia was common and resulted in treatment being stopped in 4 patients. Other adverse effects with oral therapy have included disturbances of liver function,[2] gastrointestinal effects,[2,3] and flushing.[2,3] There has been a report of exanthema in a patient receiving dimethyl fumarate for lichen planus.[4]

1. Hoefnagel JJ, *et al.* Long-term safety aspects of systemic therapy with fumaric acid esters in severe psoriasis. *Br J Dermatol* 2003; 149: 363–9.
2. Nieboer C, *et al.* Systemic therapy with fumaric acid derivates: new possibilities in the treatment of psoriasis. *J Am Acad Dermatol* 1989; 20: 601–8.
3. Mrowietz U, *et al.* Treatment of psoriasis with fumaric acid esters: results of a prospective multicentre study. *Br J Dermatol* 1998; 138: 456–60.
4. Guenther CH, *et al.* Macular exanthema due to fumaric acid esters. *Ann Pharmacother* 2003; 37: 234–6.

Pharmacokinetics

Dimethyl fumarate is rapidly hydrolysed to its active metabolite, monomethyl fumarate, by esterases in the gastrointestinal tract, blood, and tissues. There is a lag time in absorption from oral modified-release preparations so that peak plasma concentrations of monomethyl fumarate occur after about 2 to 2.5 hours. It is metabolised further through the citric acid cycle, with the exhalation of carbon dioxide being the main route of elimination; trace amounts of monomethyl fumarate are found in urine. The terminal half-life of monomethyl fumarate is about 1 hour.

References.

1. Litjens NHR, *et al.* Pharmacokinetics of oral fumarates in healthy subjects. *Br J Clin Pharmacol* 2004; 58: 429–32.
2. Rostami-Yazdi M, *et al.* Pharmacokinetics of anti-psoriatic fumaric acid esters in psoriasis patients. *Arch Dermatol Res* 2010; 302: 531–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ingepsort; *USA*: Tecfidera.

Multi-ingredient Preparations. *Ger.*: Fumaderm; *Indon.*: Diasulin; *Venez.*: Diamel.

Homoeopathic Preparations. *Ger.*: Hepar comp; Zitronensaure-zyklus-Heel.

Glycolic Acid

Ácido hidroxiacético; Glicólico, ácido; Hydroxyacetic Acid; Гидроксиуксусная Кислота; Гликолевая Кислота.

Hydroxyethanoic acid.

$C_2H_4O_3$=76.05

CAS — 79-14-1.

UNII — 0WT12SX38S.

Profile

Glycolic acid is an alpha hydroxy organic acid with keratolytic and humectant properties. It has been used in topical preparations for hyperpigmentation (see Pigmentation Disorders, p. 1687.2) and photodamaged skin (see Photoageing, p. 1686.2). Glycolic acid derivatives with similar properties and uses include ammonium glycolate and guanidine glycolate.

Other alpha hydroxy acids (fruit acids) that have been used similarly include citric acid (p. 2480.3), lactic acid (p. 2539.1), malic acid (p. 2549.2), and mandelic acid (p. 320.3). Preparations containing mixed alpha hydroxy acids from natural sources have also been used.

Sun protection is advised if topical alpha hydroxy acids are used.

Reviews.

1. Kornhauser A, *et al.* Applications of hydroxy acids: classification, mechanisms, and photoactivity. *Clin Cosmet Investig Dermatol* 2010; 3: 135–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alfabase 8; Geloforte; Glicoisdin; Gligel; Hidrofrut; Ikeriane; Lactrime; Lipomax; Loxidil; Vansame G; *Braz.*: Demelan; *Canad.*: Reversa; *Chile*: Neosolets;

Scrub-Atlas; Unitone 4; *Fr.*: Ikeriane; *Ger.*: Dr Wolff's acne attack; *Hong Kong*: Glyderm†; *India*: Glyaha; Glyco-6; Glyco-A; Glylak; Golic; *Indon.*: Exfoliac†; Glycare†; Glycore; *Ital.*: NeoStrata; Shakti; *Mex.*: Glicoderm; Glicolic; Nova Derm; *Philipp.*: Teranex; *Singapore*: Glyderm†.

Multi-ingredient Preparations. *Arg.*: Cellskinlab C + AHA; Cleanance; Control Acne; Diacneal; Hidroskin; Keracnyl; Keracnyl; Lactocrem; Melacler; Negacne; Neoquin Forte; Neoquin; NeoStrata Gel Despigmentante; NeoStrata; Percutalfa; Puraplus; Purasoft; Recover Whitening; Revi-Atlas; Revital; Scrub-Atlas; Vansame GS; Vansame Plus; *Austral.*: Elucent Skin Refining Day Cream; NeoStrata; Sunsense Anti Ageing Face; *Braz.*: Glyquin; *Canad.*: Biobase-G; Glyquin XM; NeoStrata Blemish Spot Gel†; NeoStrata†; Reversa UV; *Chile*: Diacneal; Glicoisdin; Glicoisdin; Keracnyl Stop Bouton; Keracnyl; NeoStrata; Neutrogena Healthy Skin†; Neutrogena Healthy Skin; Neutrogena Limpiadora†; Normaderm Barra de Limpieza; Normaderm Exfoliante; Normaderm Gel de Limpieza; Normaderm Tonico Astringente; Photoderm AKN†; Revi-Atlas; Teen Derm K; Ureadin Forte; *Fr.*: Aniospray 29†; Cleanance K; Day Peel†; Kelual DS; Keracnyl eau nettoyante†; Keracnyl stop bouton; Keracnyl; Keracnyl; Keracnyl; Kertyol PSO; Kertyol-S†; Melascreen Depigmentant; Night Peel†; Node K; Seborheane†; *Hong Kong*: Glyquin†; SunSense Anti-ageing Face Matte; *India*: Demelan; Glyaha-HQ; Glyaha-HQSP; Glyaha-KOJ; Glyaha-VIT; *Indon.*: Exfoliac†; Interquin Plus; *Ital.*: Acnesan; Biophase Shampoo; Lightening; Neoceuticals Spot Treatment†; Phytic Acid; Same-Seb Beta; *Malaysia*: Exfoliac Sunblock; TDF AHA Facial Wash for Oily/Acne Prone Skin; TDF AHA Oily & Acne Solution; *Mex.*: Glicolic H; Nova Derm Facial Lightening; *Port.*: Biodin Sebo Care†; U Lactin†; Ureadin Forte; Ureadin; *Singapore*: Glyquin XM†; Glyquin†; Nu-Derm Exfoderm Forte; Percutalfa; Purifying Gel; *Turk.*: NeoStrata Akne; NeoStrata Hiperpigmentasyon; NeoStrata; *USA*: Glyquin XM; *Venez.*: Diacneal; Photoderm AKN.

Homosalate *(BAN, rINN)*

Homomenthyl Salicylate; Homosalato; Homosalatum; Гомосалат.

3,3,5-Trimethylcyclohexyl salicylate.

$C_{16}H_{22}O_3$=262.3

CAS — 118-56-9.

UNII — V06SV4M95S.

NOTE. Eusolex HMS and Neo-Heliopan HMS are trade names that have been used for homosalate.

Pharmacopoeias. In *US.*

USP 36: (Homosalate). Store in airtight containers.

Profile

Homosalate, a substituted salicylate, is a sunscreen (p. 1681.3) with actions similar to those of octisalate (p. 1715.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Coppertone Oil-Free Sunscreen; *USA*: Coppertone Moisturizing; Tropical Blend Dark Tanning; Tropical Blend Dry Oil.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Hydroquinone

Hidrokinon; Hidroquinol; Hidroquinona; Hydrochinon; Hydrochinonum; Quinol; Teequinol; Гидрохинон.

1,4-Benzenediol.

$C_6H_6O_2$=110.1

CAS — 123-31-9.

ATC — D11AX11.

ATC Vet — QD11AX11.

UNII — XV74C1N1AE.

NOTE. Do not confuse with Hydroquinine (p. 2529.2).

Pharmacopoeias. In *US.*

USP 36: (Hydroquinone). Fine white needles which darken on exposure to light and air. Soluble 1 in 17 of water, 1 in 4 of alcohol, 1 in 51 of chloroform, and 1 in 16.5 of ether. Store in airtight containers. Protect from light.

Uses and Administration

Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. Hydroquinone is used topically as a depigmenting agent for the skin in hyperpigmentation conditions (p. 1687.2) such as chloasma (melasma), freckles, and lentigines (liver spots). Concentrations of 2 to 4% are commonly used; higher concentrations may be very irritant and increase the risk of ochronosis. It may be several weeks before any effect is apparent but depigmentation may last for 2 to 6 months after stopping. Application of hydroquinone should stop if there is no improvement after 2 months. Hydroquinone should be applied twice daily only to intact skin which should be protected from sunlight to reduce repigmentation. A preparation containing hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% may be applied once daily at night in the treatment of chloasma (melasma). Hydroquinone preparations often include a sunscreen or a sunblocking basis.

Hydroquinone is also used as an antoxidant in topical preparations and in photographic developers.

Adverse Effects, Treatment, and Precautions

Topical hydroquinone may cause transient erythema and a mild burning sensation. Occasionally hypersensitivity has occurred and US licensed product information recommends skin testing before use. Hydroquinone should not be applied to abraded or sunburnt skin. It should not be used to bleach eyelashes or eyebrows and contact with the eyes should be avoided as it may produce staining and corneal opacities. High concentrations or prolonged use may produce a blue-black hyperpigmentation (ochronosis) or pigmented colloid milium. The systemic effects of hydroquinone and their treatment are similar to those of phenol (see p. 1764.2) but tremors and convulsions may also occur.

Carcinogenicity. There is some evidence from *animal* studies that hydroquinone might be carcinogenic (see Effects on the Skin, below).

Effects on the liver. Toxic hepatitis in a radiographer was attributed to occupational exposure to hydroquinone fumes from the developing medium used in the darkroom.[1] However, it has been pointed out[2] that hydroquinone is not volatile under normal conditions of use and that surveillance of 879 people engaged in the manufacture and use of hydroquinone from 1942 to 1990 found no association between toxic hepatitis and hydroquinone exposure.

1. Nowak AK, *et al.* Darkroom hepatitis after exposure to hydroquinone. *Lancet* 1995; **345**: 1187.
2. O'Donaghue JL, *et al.* Hydroquinone and hepatitis. *Lancet* 1995; **346**: 1427–8.

Effects on the skin. The incidence of exogenous ochronosis (blue-black hyperpigmentation) in a survey of black South African patients was found to be 15% in males and 42% in females with 69% of affected individuals admitting to using hydroquinone-containing preparations.[1] This was considered to be more consistent with a toxic effect of a drug with a low therapeutic index, rather than an idiosyncratic reaction. The data revealed that even preparations with hydroquinone 2% or less with a sunscreen produced ochronosis. Ochronosis usually became apparent after about 6 months of use and, once established, was probably irreversible. Patients may initially use skin lighteners for cosmetic purposes but once ochronosis develops they may fall into the 'skin lightener trap' as they use other hydroquinone preparations to remove the disfigurement.[1] Treatment of exogenous ochronosis is based on stopping the use of hydroquinone, but it may take years for any improvement to be apparent. There are a few reports of benefit from topical tretinoin, dermabrasion, and laser therapy, but these are far from established therapies.[2] Reversible brown discoloration of the nails has also been reported after the use of skin lighteners containing hydroquinone.[3-5]

In addition to the risk of ochronosis it has been suggested that, based on *animal* studies, long-term use of hydroquinone might be carcinogenic.[6] In the USA, preparations containing up to 2% hydroquinone may be sold without prescription, but in 2006, based on data regarding potential carcinogenicity and reports of ochronosis, the FDA proposed to reclassify these products as drugs and make them available by prescription only.[7] In Europe the use of hydroquinone in cosmetic preparations for skin lightening is already banned, but it is still available for prescription as a medicine.[6]

1. Hardwick N, *et al.* Exogenous ochronosis: an epidemiological study. *Br J Dermatol* 1989; **120**: 229–38.
2. Levin CY, Maibach H. Exogenous ochronosis: an update on clinical features, causative agents and treatment options. *Am J Clin Dermatol* 2001; **2**: 213–17.
3. Mann RJ, Harman RRM. Nail staining due to hydroquinone skin-lightening creams. *Br J Dermatol* 1983; **108**: 363–5.
4. Ozluer SM, Muir J. Nail staining from hydroquinone cream. *Australas J Dermatol* 2000; **41**: 255–6.
5. Parlak AH, *et al.* Discolouration of the fingernails from using hydroquinone skin-lightening cream. *J Cosmet Dermatol* 2003; **2**: 199–201.
6. Kooyers TJ, Westerhof W. Toxicology and health risks of hydroquinone in skin lightening formulations. *J Eur Acad Dermatol Venereol* 2006; **20**: 777–80.
7. FDA. Skin bleaching drug products for over-the-counter human use; proposed rule. *Fed Regist* 2006; **71**: 51146–55. Available at: http://edocket.access.gpo.gov/2006/E6-14263.htm (accessed 23/07/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Claripel; *Braz.*: Claquinona; Claripel; Cleankinol; Hidropeek; Solaquin; *Canad.*: Active 4; Creme Blanchissante; Eldopaque; Eldoquin; Esoterica Regular; Esoterica Unscented†; Lustra; Nuderm; Palmer's Skin Success; Rodan & Fields Proactiv Skin Lightening†; Seequin; Ultraquin Plain; Vantex; *Chile*: Etnoderm; Unitone 4; *China*: Qian Bai (千白); *Fr.*: Effasun Hydroquin; *Gr.*: Eldopaque; *Hong Kong*: Derma-Rx Lightener†; Domina; Eldopaque; Eldoquin; Solaquin†; *India*: Claripel Plus; Depig; Eslite; Eukroma; Hyde; Hyne; Melalite Forte; Melanorm; *Indon.*: Bioquin; Eqinon; Mediquin; Melanox; Melaskin†; Pigmet†; Pylaquin†; Qutifar†; Skinox; Vitaquin; *Israel*: Esomed; *Malaysia*: Eldopaque; Eldoquin†; Melashine; *Mex.*: Crema Blanca; Eldopaque; Eldoquin; Hidroquin; Melanex; Quinoret Forte; *NZ*: Eldoquin†; *Port.*: Pigmentasa; *Singapore*: Eldopaque; Eldoquin; Nu-Derm Blender; Nu-Derm Clear; Polyquin; Solaquin†; *Spain*: Despigmental; Hidroquilaude; Licoforte; Licostrata; Melanasa; Nadona; Pigmentasa; Solumelan; *Thai.*: Clariderm†; Delanin; Delet†; Persatina; *Turk.*: Expigment; *UK*: Eldopaque; Eldoquin; Solaquin; *USA*: Aclaro; Claripel†; Eldopaque; Eldoquin; EpiQuin; Esoterica Regular; Lustra; Solaquin.

Multi-ingredient Preparations. *Arg.*: Melacler; Melasmax; Neoblanc; Neoquin Forte; Neoquin; NeoStrata Gel Despigmentante; Solaquin Forte; Tri-Luma; Trimegtante; *Austral.*: Superfade Original†; *Braz.*: Glyquin; Hormoskin; Suavicid; Tri-Luma; Triderm; Vitacid Plus; *Canad.*: Continuum Unifying; Drula Fade; Esoterica Facial; Esoterica Sunscreen Fade; Glyquin XM; Lustra-AP; NeoStrata HQ Plus; NeoStrata HQ†; Nuderm Sunfader; Solaquin Forte; Sunbalance; Ultraquin Hydroquinone with Sunscreens; *Chile*: Clasifel; NeoStrata; Tri-Luma; *Ger.*: Pigmanorm; *Hong Kong*: Glyquin†; Superfade; Tri-Luma; *India*: A-Ret HC; Acsolve-H; Brite; Depig-TM; Eukroma-SG; Eveglow; Glyaha-HQ; Glyaha-HQSP; Glyaha-KOJ; Hyclean; Lite-Up; M-Lite; Melacare; Melacut; Melalite Plus; Melalite-XL; Melalite; Melalong; Melanorm-HC; Multi-HTM; *Indon.*: Hidrogel†; Interquin Plus; Interquin; Meladerm; Nu-Derm Sunblock†; Refaquin; *Malaysia*: Solaquin Forte†; Tri-Luma; *Mex.*: Clasifel; Glicolic H; Nova Derm Facial Lightening; Quinoret; Solaquin; Tri-Luma; *Philipp.*: Tri-Luma; *Singapore*: Glyquin XM†; Glyquin†; Nu-Derm Sunfader†; Tri-Luma; *Switz.*: Pigmanorm; *Thai.*: Tri-Luma; *Turk.*: Metamorfoz; NeoStrata Hiperpigmentasyon; *USA*: Esoterica Facial and Sunscreen; Esoterica Fade Cream; Glyquin XM; Solaquin Forte; Solaquin Forte; Tri-Luma; *Venez.*: Tri-Luma.

Pharmacopoeial Preparations

USP 36: Hydroquinone Cream; Hydroquinone Topical Solution.

Ichthammol *(BAN)*

Ammonii Bituminosulfonas; Ammonii Sulfogyrodalas; Ammonio Sulfoittiolato; Ammonium Bithiolicum; Ammonium Bitumenosulfonicum; Ammonium Bituminosulphonate; Ammonium Ichthosulphonate; Ammonium Sulfobituminosum; Ammonium Sulpho-Ichthyolate; Ammoniumbituminosulfonat; Amoniowy sulfobituminian; Bithiolate Ammonique; Bithyol; Bitiol; Bitiolato amónico; Bitomol; Bituminol; Ichtammol; Ichtamolis; Ichthammolum; Ichthamol; Ichthosulphol; Ichthyol; Ichthyolammonium; Ictamol; Ictiolsulfonato amónico; Ihtamol; Iktammol; Iktammoli; Sulfobituminato amónico; Sulfoictiolato amónico; Ихтаммол; Ихтиол.

CAS — 8029-68-3.

UNII — NQ14646378.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US.*

Ph. Eur. 8: (Ichthammol). A dense blackish-brown liquid. It is obtained by distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with ammonia. It contains not less than 4.5% and not more than 7.0% of total ammonia, not less than 10.5% of organically combined sulfur, calculated with reference to the dried substance, and not more than 20% of the total sulfur in the form of sulfates.

Miscible with water and with glycerol; slightly soluble in alcohol, in fatty oils, and in liquid paraffin; forms homogeneous mixtures with wool fat and soft paraffin.

USP 36: (Ichthammol). A reddish-brown to brownish-black viscous fluid with a strong characteristic empyreumatic odour. It is obtained by the destructive distillation of a bituminous schist, sulfonation of the distillate, and neutralisation of the product with ammonia. It yields not less than 10.0% of total sulfur and not less than 2.5% of ammonia. Miscible with water, with glycerol, and with fixed oils and fats. Partially soluble in alcohol and in ether.

Incompatibility. Ichthammol is incompatible with wool alcohols.

Profile

Ichthammol has slight bacteriostatic properties and is used in many topical preparations, for a variety of skin disorders; it has also been used in suppositories for anorectal disorders.

Ichthammol is often used with zinc oxide in medicated bandages for chronic lichenified eczema (p. 1684.1). Ichthammol may be slightly irritant to the skin and there have been rare reports of hypersensitivity.

Light Ammonium Bituminosulfonate (Ammoniumbituminosulfonat Hell) is produced from the light distillate fraction of shale oil.

Ammoniumsulfobitol, an ammonium bituminosulfonate similar to ichthammol but with a low sulfur content, was commercially available as Tumenol Ammonium.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Egoderm; *Austria*: Ichtho-Bad; Ichtholan; *Belg.*: Bithiol; Poudre Velours†; *Cz.*: Ichtoxyl; *Ger.*: Ichtho-Bad; Ichtholan spezial; Ichtholan; Ichthyol; Thiobitum; *Indon.*: Ichtiyol-Zalf; *Ital.*: Ittiolo; *Neth.*: Daro Trekzalf; Trekzalf; *Switz.*: Bitumol; Ichtho-Bad; Ichtholan; *Turk.*: Ihtiyol; Pomat Ichthyole†; Pommade Ichthyole†; *Ukr.*: Fitoval Antidandruff (Фітовал Проти Перхоти).

Multi-ingredient Preparations. *Arg.*: Cicatrina; *Austral.*: Egoderm; Ichthopaste; *Austria*: Aknemycin compositum; Delta-Hadensa; Hadensa; Hadensa; Inotyol; Inotyol; *Belg.*: Antipiol†; Inotyol; *Canad.*: Ichtopaste; *Chile*: Kertyol; Selegel; *Cz.*: Pityol; Saloxyl; *Denm.*: Inotyol; *Fin.*: Hadensa†; Hadensa; *Fr.*: Anaxeryl; Gelictar Fort†; Inotyol; Node DS; Oxythyol; Phytheol Force†; Selegel†; Squaphane; *Ger.*: Aknemycin†; *Gr.*: Ichthocortex; *Hong Kong*: Egoderm; Egoderm; *India*: Exsora; Itchasia; *Israel*: Aknemycin; Inotyol; *Ital.*: Antiemorroidali†; Dermatar; Ichthopaste; Ityolate CE; Tricoderm F; *Malaysia*: Egoderm; Egoderm; *Norw.*: Inotyol; *NZ*: Egoderm; *Pol.*: Neo-Tormentil; Tormentile Forte; Tormentiol; *Port.*: Efluvium Anti-caspa†; Efluvium Anti-seborreico†; Pansebase Composto; Secpel Composto†; *Rus.*: Bethiol (Бетиол); *S.Afr.*: Antipeol; *Singapore*: Egoderm; Egoderm; *Spain*: Hadensa; Ictiomen; *Swed.*: Inotyol; *Switz.*: Akne-Mycin†; Bain extra-doux; Furodermal†; Radix†; *Turk.*: Hedensa; *UK*: Antipeol; Ichthopaste; Ichthaband; St James Balm; *Ukr.*: Prostalin (Простилин); *USA*: Boil Ease; Boyol Salve; *Venez.*: Node DS.

Homoeopathic Preparations. *Canad.*: Cutisitum†; *Ger.*: Hewelymphon N†.

Pharmacopoeial Preparations
BP 2014: Zinc and Ichthammol Cream;
USP 36: Ichthammol Ointment.

Ictasol *(USAN)*

Ichtasol; Ichthyol-Natrium Heil; Light Sodium Bituminosulphonate; Natrium Sulfobituminosum Decoloratum; Sulfobituminato sódico; Sulfobituminato sódico decolorado.

$C_{28}H_{36}Na_2O_6S_3$=610.7

CAS — 12542-33-5; 1340-06-3.
ATC — D10BX01.
ATC Vet — QD10BX01.

Profile

Ictasol is a sodium bituminosulfonate produced from the light distillate fraction of shale oil. Sodium bituminosulfonate is obtained by the destructive distillation of certain bituminous schists, sulfonation of the distillate, and neutralisation of the product with sodium hydroxide.

Ictasol has similar properties to ichthammol (p. 1705.3) and is used in many preparations for a variety of skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Crino Cordes; Lavichthol†; Solutio Cordes; *Ger.*: Aknichthol; Ichthoderm; Ichtholan T; Ichthosin; Ichthraletten; Leukichtan; Solutio Cordes.

Multi-ingredient Preparations. *Arg.*: Selegel; *Austria*: Aknichthol; Ichthalgan forte; Leukichtan; *Fr.*: I-Soft; Kertyol PSO; Node DS+; Sebosquam†; *Ger.*: Aknederm Neu†; Aknichthol; Ichthocortin; Ichthoseptal†; Pelvichthol N†; *Switz.*: Aknichthol.

Iscotrizinol *(USAN)*

Diethylhexyl Butamido Triazone; Diethylhexylbutamido Triazone; Dioctylbutamidotriazone.

Bis(2-ethylhexyl) 4,4'-[(6-[[4-(*tert*-butylcarbamoyl)phenyl]amino)-1,3,5-triazine-2,4-diyl)diimino]dibenzoate.

$C_{44}H_{59}N_5O_5$=766.0

CAS — 154702-15-5.
UNII — 2UTZ0QCB64.

NOTE. Uvasorb HEB is a trade name that has been used for iscotrizinol.

Profile

Iscotrizinol is used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Eucerin Ninos; Eucerin Solar†; Eucerin; Fotoprotector Isdin Dry Oil†; Nutraisdin; *Fr.*: Sun LEB; *Thai.*: Eucerin Sun Sensitive Skin†; Sebamed Multi Protect Suncream.

Isopropyldibenzoylmethane

Isopropildibenzoilmetano; Изопропилдибензоилметан.

1-[4-(1-Methylethyl)phenyl]-3-phenyl-1,3-propanedione.

$C_{18}H_{18}O_2$=266.3

CAS — 63250-25-9.

Profile

Isopropyldibenzoylmethane, a substituted dibenzoylmethane, is a sunscreen (p. 1681.3) with actions similar to those of avobenzone (p. 1695.1). It is effective against UVA light (for definitions, see p. 1685.3).

Isotretinoin *(BAN, USAN, rINN)*

13-*cis*-Retinoic Acid; Isotretinoiini; Isotretinoína; Isotrétinoïne; Isotretinoinum; Izotretinoin; Izotretinoinas; Izotretynoina; Ro-4-3780; Изотретиноин.

(13*Z*)-15-Apo-β-caroten-15-oic acid; (2*Z*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-tetraenoic acid.

$C_{20}H_{28}O_2$=300.4

CAS — 4759-48-2.
ATC — D10AD04; D10BA01.
ATC Vet — QD10AD04; QD10BA01.
UNII — EH28UP18IF.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Isotretinoin). A yellow or light orange, crystalline powder. Practically insoluble in water; slightly soluble in alcohol; soluble in dichloromethane. It is sensitive to air, heat, and light, especially in solution. Store in airtight containers under an inert gas. Protect from light. It is recommended that the contents of an opened container be used as soon as possible and that any unused part be protected by an atmosphere of an inert gas.

USP 36: (Isotretinoin). Yellow crystals. Practically insoluble in water; sparingly soluble in alcohol, in isopropyl alcohol, and in macrogol 400; soluble in chloroform. Store in airtight containers under an atmosphere of an inert gas. Protect from light.

Uses and Administration

Isotretinoin is a retinoid. It is the *cis* configuration of tretinoin (p. 1725.2), which is the acid form of vitamin A (p. 2098.3). Isotretinoin is given orally for the treatment of severe acne (below) that has not responded to other measures; it is also applied topically in milder forms of acne. It is not indicated for uncomplicated adolescent acne, and is not licensed for prepubertal acne (but see also Administration in Children, below, for use in infantile acne). Isotretinoin has also been tried in other skin disorders (p. 1707.2) and in some forms of neoplastic disease (p. 1707.1).

In the UK and several other countries the initial oral dose of isotretinoin for acne is 500 micrograms/kg daily, although in the USA initial doses of up to 1 mg/kg daily are permitted. The dose is given with food once daily or in two divided doses and adjusted if necessary up to 1 mg/kg daily according to response and adverse effects. Patients intolerant to the initial dose may be able to continue treatment at a lower dose, but there is a higher risk of relapse. Doses up to 2 mg/kg daily are permitted in the USA and some other countries for patients whose disease is very severe or mainly on the body instead of the face. A lower starting dose has been recommended for patients with severe renal impairment (see p. 1707.1).

Acute exacerbation of acne is occasionally seen during the initial period, but usually subsides within 7 to 10 days on continued treatment. Treatment should continue for 15 to 24 weeks or until the total cyst count has decreased by over 70%. Long-term remission and relapse rates are related to total dose, and additional benefit is not expected beyond a cumulative dose of 120 to 150 mg/kg. Improvement may continue for several months after stopping treatment; prolonged remissions can occur.

Repeat courses are not normally recommended but occasionally they may be required. However, since acne may continue to improve after stopping isotretinoin, there must be at least a 2-month drug-free period before starting repeat treatment.

For the topical treatment of acne a gel containing 0.05% of isotretinoin is applied sparingly once or twice daily. A therapeutic response may not be evident for 6 to 8 weeks.

General reviews.

1. DiGiovanna JJ. Systemic retinoid therapy. *Dermatol Clin* 2001; 19: 161–7.
2. Ellis CN, Krach KJ. Uses and complications of isotretinoin therapy. *J Am Acad Dermatol* 2001; 45 (suppl): S150–S157.
3. Vivat-Hannah V, Zusi FC. Retinoids as therapeutic agents: today and tomorrow. *Mini Rev Med Chem* 2005; 5: 755–60.
4. Njar VC, *et al.* Retinoids in clinical use. *Med Chem* 2006; 2: 431–8.

Acne. The retinoids play an important role in the treatment of acne (p. 1682.2). Isotretinoin reduces sebum excretion with a subsequent reduction in growth of *Propionibacterium acnes*; it also normalises the differentiation of keratinocytes, which has a comedolytic effect, and appears to have a direct anti-inflammatory effect.[1-3] The main indication for oral isotretinoin therapy is severe forms of acne (such as conglobate or nodulocystic acne or acne at risk of permanent scarring) that is unresponsive to other therapy including systemic antibacterials. Some argue,[4,5] however, that oral isotretinoin should be considered for first-line treatment in other cases, such as less severe acne that has the potential to cause scarring or acne that is causing severe psychological distress. Most patients remain free of their disease after a single course of isoretinoin, or have a mild recurrence that responds to other treatments to which it was previously resistant. A minority will relapse and those at higher risk include patients less than 16 years of age, those with severe acne on the trunk, and adult women.[2] Cumulative dose, rather than daily dose, appears to be an important factor in achieving stable remission.[4] To avoid relapse, a course of therapy to a cumulative dose of 120 to 150 mg/kg is required.[2] This usually equates to a course of 5 to 6 months using daily doses of 0.5 to 1 mg/kg. One group suggests[4] that treatment should be continued for 2 months after complete clearing of acne to avoid recurrence, and that higher cumulative doses (up to 200 mg/kg) might be needed in some cases, such as those showing clear signs of ongoing improvement when a cumulative dose of 150 mg/kg has been reached. In patients who do relapse, repeat courses may be indicated.[2,3] However, improvement may continue for several months after withdrawal and at least 2 months should elapse before determining whether further treatment is necessary. There is evidence to suggest that patients who repeatedly relapse after stopping standard isotretinoin therapy may benefit from continuous use of very low doses of isotretinoin, such as 250 or 500 micrograms/kg daily taken every 4th week for 6 months, 100 micrograms/kg daily, or a single dose of 20 mg once or twice a week.[6] Low-dose regimens have also been tried instead of standard isotretinoin doses for persistent moderate or severe acne. A dose of 20 mg daily for 6 months has produced significant improvement or complete remission in moderate acne.[7] However, prolonged use of low-dose regimens is needed to achieve a cumulative dose of 120 mg/kg and reduce the risk of relapse.[8] Isotretinoin has also been used for the treatment of acne associated with immunosuppressive therapy in transplant recipients.[9,10]

Isotretinoin is also used topically for acne. Although it has no sebosuppressive effect and only a weak direct anti-inflammatory effect by this route[1] its comedolytic effect makes unplugged follicles less anaerobic, reducing *P. acnes* growth and associated inflammation.[11] Topical isotretinoin appears to have a similar efficacy to tretinoin, but may be better tolerated.[3]

Isotretinoin is not licensed for the treatment of prepubertal acne because of the risk of adverse effects including early epiphyseal closure, but see also Administration in Children, below.

1. Gollnick H. Current concepts of the pathogenesis of acne: implications for drug treatment. *Drugs* 2003; 63: 1579–96.
2. James WD. Acne. *N Engl J Med* 2005; 352: 1463–72.
3. Chivot M. Retinoid therapy for acne: a comparative review. *Am J Clin Dermatol* 2005; 6: 13–19.
4. Cooper AJ. The Australian Roaccutane Advisory Board. Treatment of acne with isotretinoin: recommendations based on Australian experience. *Australas J Dermatol* 2003; 44: 97–105.
5. Dréno B, *et al.* An expert view on the treatment of acne with systemic antibiotics and/or oral isotretinoin in the light of the new European recommendations. *Eur J Dermatol* 2006; 16: 565–71.
6. Palmer RA, *et al.* Microdose' isotretinoin. *Br J Dermatol* 2000; 143: 205–6.
7. Amichai B, *et al.* Low-dose isotretinoin in the treatment of acne vulgaris. *J Am Acad Dermatol* 2006; 54: 644–6.
8. Mandekou-Lefaki I, *et al.* Low-dose schema of isotretinoin in acne vulgaris. *Int J Clin Pharmacol Res* 2003; 23: 41–6.
9. Tam M, Cooper A. The use of isotretinoin in a renal transplant patient with acne. *Br J Dermatol* 1987; 116: 463.
10. Bunker CB, *et al.* Isotretinoin treatment of severe acne in posttransplant patients taking cyclosporine. *J Am Acad Dermatol* 1990; 22: 693–4.
11. Goulden V. Guidelines for the management of acne vulgaris in adolescents. *Pediatr Drugs* 2003; 5: 301–13.

Administration in children. Oral isotretinoin is licensed in most countries for use from 12 years of age where appropriate, but it is not licensed for the treatment of prepuber-

tal acne because of the risk of adverse effects including early epiphyseal closure. However, it has been used orally with some success in nodulocystic infantile acne when topical preparations and antibacterial therapies have not been effective.[1-4] A range of doses have been used, sometimes influenced by the dosage form available, but in general doses have been similar to those used in older patients. For example, the *BNFC* considers that children aged 1 month to 2 years with severe infantile acne may be given 200 micrograms/kg once daily increased, if necessary, to 1 mg/kg daily (in 1 or 2 divided doses) for 16 to 24 weeks; the maximum cumulative dose per course is 150 mg/kg. As there are no suitable licensed oral products for children, isotretinoin liquid capsules have been opened and the contents mixed with a drink[1,2] or soft food[3] immediately before use to make administration easier. One report[3] described freezing the capsule so that it could be cut more easily to the required dose, which could then be concealed in food.

Topical isotretinoin is not licensed in the UK for use in children although the *BNFC* mentions use of the 0.05% gel applied once or twice daily for acne vulgaris.

For mention of the investigation of isotretinoin in children with neuroblastoma, see Malignant Neoplasms, below.

1. Mengesha YM, Hansen RC. Toddler-age nodulocystic acne. *J Pediatr* 1999; 134: 644–8.
2. Sarazin F, *et al.* Treatment of an infantile acne with oral isotretinoin. *Eur J Dermatol* 2004; 14: 71–2.
3. Barnes CJ, *et al.* A practical approach for the use of oral isotretinoin for infantile acne. *Pediatr Dermatol* 2005; 22: 166–9.
4. Torrelo A, *et al.* Severe acne infantum successfully treated with isotretinoin. *Pediatr Dermatol* 2005; 22: 357–9.

Administration in renal impairment. Although renal impairment does not affect the pharmacokinetics of isotretinoin, licensed UK product information suggests that patients with severe renal impairment being treated with oral isotretinoin for acne should be started at a lower dose, such as 10 mg daily. It may be gradually increased up to 1 mg/kg daily as tolerated.

Malignant neoplasms. Retinoids such as isotretinoin have been studied in the treatment of various neoplastic or preneoplastic disorders. Although oral tretinoin is used for remission induction in acute promyelocytic leukaemia (see p. 1725.3), other retinoids do not have an established role in the treatment of cancer. There may, however, be a place for the use of retinoids in the chemoprevention of some malignancies.

There has been particular interest in the potential for retinoids to prevent the formation of *skin cancers* (p. 714.1) in patients at increased risk. Maintenance immunosuppression may increase the incidence of pre-malignant and malignant skin lesions in solid organ transplant recipients; large numbers of lesions can develop and tend to be more aggressive than those in the general population.[1] Although there has been some investigation in cardiac transplant recipients, most case reports and some small studies have involved renal transplant patients. Oral acitretin has been reported to reduce the number of actinic keratoses and reduce the development of new basal and squamous cell carcinomas in these patients.[1-4] Other patients at increased risk of skin cancers who may benefit from prophylactic retinoid therapy include those with xeroderma pigmentosum and naevoid basal cell carcinoma syndrome; oral isotretinoin, rather than acitretin, has been tried in such patients.[5] Retinoids might also be considered in others who have already developed nonmelanoma skin cancers, such as those with conditions requiring maintenance immunosuppression, chronic lymphocytic leukaemia or non-Hodgkin's lymphoma, severe photodamage of the skin, and those with squamous cell carcinoma at high risk of metastasis or that has already metastasised.[5]

Since retinoids suppress rather than cure skin cancer, rebound occurs when the retinoid is stopped and long-term therapy is needed. There is some concern about the risks of such long-term use, particularly on plasma lipids and bone, and monitoring has been recommended.[1,4,5] The mucocutaneous adverse effects that commonly occur can affect patient acceptance during long-term use; mucocutaneous effects may be more severe with isotretinoin, but hair loss may be more extensive with acitretin.[4,5] Gradual dose escalation to an effective dose can be used to minimise these mucocutaneous effects. One example using isotretinoin starts with a dose of 250 micrograms/kg on alternate days for a month, increased to 250 micrograms/kg daily for the second month, then to 500 micrograms/kg daily for the third month; the dose is then adjusted as tolerated.[5] As there are risks of teratogenicity with retinoids, isotretinoin is preferred for women of child-bearing potential because of its shorter half-life.[4,5] For acitretin doses that have been used, see p. 1691.1.

Topical application of retinoids has also been tried for chemoprevention of skin cancers. Topical tretinoin has been used on actinic keratoses in organ transplant recipients, but results have been mixed and may depend on dose. If squamous cell carcinomas are present, however, systemic retinoids should be considered.[5]

Retinoids have been studied in the chemoprevention of primary disease recurrence and second primary tumours after treatment for *squamous cell carcinoma of the head and neck* (p. 708.1) but results have been mixed and limited by resistance and toxicity.[6] A large placebo-controlled study[7] has also reported that low-dose oral isotretinoin (30 mg daily for 3 years with an additional 4 years of follow-up) did not reduce the rate of second primary tumours or death in patients who had been treated for early stage head and neck squamous cell carcinoma. There has also been some interest in the use of retinoids, given orally (isotretinoin) or topically (isotretinoin or tretinoin), in the management of *oral leucoplakia*, which can be pre-malignant (see under Bleomycin, p. 750.3). However, despite reports of beneficial response, relapse frequently occurs on stopping retinoid therapy.[6,8]

Oral isotretinoin has been studied as continuation therapy in children with high-risk *neuroblastoma* that had responded to intensive chemotherapy. One study[9] found improved survival with 6 cycles of isotretinoin given for 14 days of each 28-day cycle. Long-term (5 year) follow-up results seem to confirm an improvement in overall survival in these patients.[10] However, another study[11] using a lower dose given daily for 4 years or until relapse found no additional benefit from isotretinoin.

1. Kovach BT, *et al.* Systemic strategies for chemoprevention of skin cancers in transplant recipients. *Clin Transplant* 2005; 19: 726–34.
2. Chen K, *et al.* Oral retinoids for the prevention of skin cancers in solid organ transplant recipients: a systematic review of randomized controlled trials. *Br J Dermatol* 2005; 152: 518–23.
3. Neuhaus IM, Tope WD. Practical retinoid chemoprophylaxis in solid organ transplant recipients. *Dermatol Ther* 2005; 18: 28–33.
4. Campbell RM, DiGiovanna JJ. Skin cancer chemoprevention with systemic retinoids: an adjunct in the management of selected high-risk patients. *Dermatol Ther* 2006; 19: 306–14.
5. Otley CC, *et al.* Chemoprevention of nonmelanoma skin cancer with systemic retinoids: practical dosing and management of adverse effects. *Dermatol Surg* 2006; 32: 562–8.
6. Smith W, Saba N. Retinoids as chemoprevention for head and neck cancer: where do we go from here? *Crit Rev Oncol Hematol* 2005; 55: 143–52.
7. Khuri FR, *et al.* Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006; 98: 441–50.
8. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. *Cancer* 2002; 95: 1258–64.
9. Matthay KK, *et al.* Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999; 341: 1165–73.
10. Matthay KK, *et al.* Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol* 2009; 27: 1007–13.
11. Kohler JA, *et al.* A randomized trial of 13-cis retinoic acid in children with advanced neuroblastoma after high-dose therapy. *Br J Cancer* 2000; 83: 1124–7.

Skin disorders. Apart from its established role in the treatment of acne (p. 1706.3), isotretinoin has been tried in many other skin disorders not responding to usual therapy.[1,2] Clinical responses to oral isotretinoin have been reported[1] in small numbers of patients with anogenital warts (p. 1689.3), rosacea (p. 1688.3), and lichen planus (p. 1685.2). Benefit has also been reported for keratinisation disorders such as Darier's disease[2] (p. 1683.2), ichthyosis[1,2] (p. 1685.1), and pityriasis rubra pilaris.[1,2] Isotretinoin is less effective than other retinoids for psoriasis[1] (p. 1688.1). Oral isotretinoin may be used for chemoprevention of skin cancers (see Malignant Neoplasms, above).

Topical isotretinoin has been used to reduce some of the signs of photoageing[3] (p. 1686.2).

1. Akyol M, Özçelik S. Non-acne dermatologic indications for systemic isotretinoin. *Am J Clin Dermatol* 2005; 6: 175–84.
2. Sehgal VN, *et al.* Isotretinoin – unapproved indications/uses and dosage: a physician's reference. *Int J Dermatol* 2006; 45: 772–7.
3. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; 65: 1061–72.

Adverse Effects

The adverse effects of isotretinoin and other oral retinoids are similar to those of vitamin A (see p. 2101.2) and are generally reversible and dose-related. The most common are dryness of the mucous membranes and skin, which can often progress to cheilitis, epistaxis, conjunctivitis, localised exfoliation including palmo-plantar exfoliation, pruritus, erythematous rash, and skin fragility. Less common effects have included hair thinning (occasionally irreversible), hirsutism, photosensitivity, changes in skin pigmentation, paronychia, nail dystrophy, pyogenic granuloma, and increased sweating. Acne can be exacerbated at the beginning of isotretinoin treatment, and there are very rare reports of acne fulminans occurring. Less common adverse effects on the eyes include corneal opacities, visual disturbances such as blurred vision and colour vision disorders, impaired night vision that may persist, photophobia, and keratitis. Papilloedema, visual disturbances, headache, and nausea and vomiting can be signs and symptoms of benign intracranial hypertension. Arthralgia, myalgia, and back pain are commonly reported, and there have been rare reports of arthritis, osteoporosis, and tendinitis. Hyperostosis and calcinosis have also occurred, particularly in patients treated with high doses of isotretinoin over long periods for keratinisation disorders. Premature closure of the epiphyses has occurred in children treated with isotretinoin. Elevation of serum triglycerides is common, and pancreatitis has occurred in patients with high concentrations; cholesterol concentrations may also be increased. Increases in hepatic enzymes, erythrocyte sedimentation rate, and blood glucose can also occur. Alterations in haematological measures are common; there have also been reports of anaemia, thrombocytopenia, and neutropenia, and very rare reports of agranulocytosis. Other effects that have been reported rarely include gastrointestinal symptoms, hepatitis, hearing impairment, drowsiness, seizures, vasculitis, and hypersensitivity reactions including anaphylaxis. Mood changes, psychotic symptoms, depression, and suicidal behaviour have occurred in patients treated with oral isotretinoin. There may also be an association with skin infections and an inflammatory bowel syndrome.

Isotretinoin and other retinoids are teratogenic.

When isotretinoin is applied topically the adverse effects are similar to those of tretinoin (see p. 1726.1).

General references.

1. Mills CM, Marks R. Adverse reactions to oral retinoids: an update. *Drug Safety* 1993; 9: 280–90.
2. Keefe M. Adverse reactions profile: retinoids. *Prescribers' J* 1995; 35: 71–6.
3. McLane J. Analysis of common side effects of isotretinoin. *J Am Acad Dermatol* 2001; 45: S188–S194.
4. Goodfield MJD, *et al.* British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; 162: 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 10/08/10)
5. Charakida A, *et al.* Safety and side effects of the acne drug, oral isotretinoin. *Expert Opin Drug Safety* 2004; 3: 119–29.
6. Goldsmith LA, *et al.* American Academy of Dermatology consensus conference on the safe and optimal use of isotretinoin: summary and recommendations. *J Am Acad Dermatol* 2004; 50: 900–906. Correction. *ibid.*; 51: 348. [dose]

Effects on the blood. Serious adverse effects on the blood have been reported rarely with oral retinoids, and are thought to be idiosyncratic in nature. There have been reports of thrombocytopenia in patients taking isotretinoin[1] and etretinate.[2,3] A few cases of agranulocytosis have involved isotretinoin[4] and acitretin.[5] In contrast, there are also reports of transient and asymptomatic thrombocytosis associated with isotretinoin[6] and tretinoin.[7,8] Leucocytosis is often associated with the retinoic acid syndrome caused by tretinoin (p. 1726.2).

1. Moeller KE, Touma SC. Prolonged thrombocytopenia associated with isotretinoin. *Ann Pharmacother* 2003; 37: 1622–4.
2. Naldi L, *et al.* Etretinate therapy and thrombocytopenia. *Br J Dermatol* 1991; 124: 395.
3. Seishima M, *et al.* Thrombocytopenia possibly induced by etretinate in a psoriatic patient. *J Dermatol* 2005; 32: 917–20.
4. Waisman M. Agranulocytosis from isotretinoin. *J Am Acad Dermatol* 1988; 18: 395–6.
5. Chave TA, *et al.* Agranulocytosis and total scalp alopecia following acitretin. *Br J Dermatol* 2003; 148: 1063–4.
6. Jansen T, Altmeyer P. Thrombocytosis induced by low-dose isotretinoin. *Int J Dermatol* 2000; 39: 956–7.
7. Losada R, *et al.* Thrombocytosis in patients with acute promyelocytic leukaemia during all-trans retinoic acid treatment. *Br J Haematol* 1996; 93: 704–5.
8. Kentos A, *et al.* All-trans retinoic acid induced thrombocytosis in a patient with acute promyelocytic leukaemia. *Br J Haematol* 1997; 97: 685.

Effects on the cardiovascular system. From 1983 to the end of 2005, Health Canada had received 29 reports of adverse cardiovascular effects in patients treated with isotretinoin, including myocardial infarction, stroke, and pulmonary embolism.[1] Thrombotic stroke has also been attributed to the use of acitretin in a woman treated for psoriasis,[2] and rare cases of myocardial ischaemia and infarction have been reported with etretinate.[3] Thromboembolic disorders have also occurred in patients given tretinoin for remission induction in acute promyelocytic leukaemia (see p. 1726.1).

There are rare reports of isotretinoin causing cardiac arrhythmias, such as sinus tachycardia with right branch bundle block[4] and atrial tachycardia.[5]

1. Springuel P, Roy G. Health Canada. Isotretinoin (Accutane): myocardial infarction, cerebrovascular and thromboembolic disorders. *Can Adverse React News* 2006; 16: 3. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v16n2-eng.php (accessed 28/07/08)
2. Royer B, *et al.* Acitretin-associated thrombotic stroke. *Ann Pharmacother* 2002; 36: 1879–82.
3. Anonymous. Reports from regulatory agencies: etretinate. *WHO Drug Inf* 1987; 1: 29.
4. Charalabopoulos K, *et al.* Two new adverse effects of isotretinoin. *Br J Dermatol* 2003; 148: 593.
5. Hasdemir C, *et al.* Isotretinoin (13-cis-retinoic acid) associated atrial tachycardia. *Pacing Clin Electrophysiol* 2005; 28: 348–9.

Effects on the eyes. Ocular adverse effects reported with oral isotretinoin have been reviewed.[1,2] Using the WHO Causality Assessment Guide of Suspected Adverse Reactions, an analysis[3] of 2449 spontaneous reports found that

decreased dark adaptation, ocular sicca, and the ocular signs and symptoms of intracranial hypertension, accounted for most of the reports that were certainly associated with isotretinoin. In some cases of intracranial hypertension the patient had also been taking other drugs, such as tetracyclines, that have also been associated with this effect. There was also a certain association between isotretinoin and abnormal meibomian gland secretion and gland atrophy, blepharoconjunctivitis, corneal opacities, decreased vision, increased tear osmolarity, keratitis, myopia, ocular discomfort and decreased tolerance to contact lenses, and photophobia. There was a probable association with reversible decreased colour vision and permanent loss of dark adaptation. Other effects that had been reported, but only possibly associated with isotretinoin, included corneal ulcers, diplopia, eyelid oedema, optic neuritis, permanent sicca, and subconjunctival haemorrhage.

There are fewer reports of ocular adverse effects with other oral retinoids. Intracranial hypertension with papilloedema, blurred vision, and headache, has been reported with acitretin, etretinate, and tretinoin.[4-6] A 1-year follow-up failed to find any evidence of ocular toxicity attributable to etretinate in 4 patients who had received long-term treatment, including 1 patient who had toxic optic neuropathy due to methotrexate and who was able to continue treatment with etretinate.[7] Ectropion has been associated with etretinate therapy in a patient.[8] Maculopathy occurred in a patient after a year of treatment with acitretin for psoriasis.[9]

1. Fraunfelder FT, *et al.* Adverse ocular reactions possibly associated with isotretinoin. *Am J Ophthalmol* 1985; 100: 534–7.
2. Fraunfelder FT, *et al.* Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol* 2001; 132: 299–305.
3. Fraunfelder FW. Ocular side effects associated with isotretinoin. *Drugs Today* 2004; 40: 23–7.
4. Colucciello M. Pseudotumor cerebri induced by all-trans retinoic acid treatment of acute promyelocytic leukemia. *Arch Ophthalmol* 2003; 121: 1064–5.
5. Guirgis MF, Lueder GT. Intracranial hypertension secondary to all-trans retinoic acid treatment for leukemia: diagnosis and management. *J AAPOS* 2003; 7: 432–4.
6. Fraunfelder FW, Fraunfelder FT. Evidence for a probable causal relationship between tretinoin, acitretin, and etretinate and intracranial hypertension. *J Neuroophthalmol* 2004; 24: 214–16.
7. Pitts JF, *et al.* Etretinate and visual function: a 1-year follow-up study. *Br J Dermatol* 1991; 125: 53–5.
8. Brenner S, *et al.* Ectropion: an adverse effect of etretinate therapy for psoriasis. *DICP Ann Pharmacother* 1990; 24: 1007.
9. Lois N, White M. Acitretin-associated maculopathy. *Arch Ophthalmol* 2004; 122: 928–30.

Effects on the gastrointestinal tract. A causal association has been suggested in cases of inflammatory bowel disease developing in patients taking oral isotretinoin.[1,2] Between 1997 and 2002 the FDA received 85 reports of Crohn's disease, ulcerative colitis, colitis, or haemorrhagic colitis attributed to isotretinoin;[3] the association was judged probable in 62 cases and possible in 23. Specific treatment, in addition to drug withdrawal, was required in 35 patients, 11 were hospitalised, and 7 underwent surgery. Rechallenge was positive in the 3 reported cases. The authors of this review suggested that isotretinoin should be used with caution in patients with a history of inflammatory bowel disease or symptoms suggestive of the condition and those who might be at increased risk because of a family history. Although there have been patients with inflammatory bowel disease who have received isotretinoin without adverse effect, there are some cases in which the condition may have been exacerbated by isotretinoin.[1,4]

1. Reniers DE, Howard JM. Isotretinoin-induced inflammatory bowel disease in an adolescent. *Ann Pharmacother* 2001; 35: 1214–16.
2. Passier JLM, *et al.* Isotretinoin-induced inflammatory bowel disease. *Neth J Med* 2006; 64: 52–4.
3. Reddy D, *et al.* Possible association between isotretinoin and inflammatory bowel disease. *Am J Gastroenterol* 2006; 101: 1569–73.
4. Godfrey KM, James MP. Treatment of severe acne with isotretinoin in patients with inflammatory bowel disease. *Br J Dermatol* 1990; 123: 653–5.

Effects on the liver. Transient slight elevations of serum concentrations of liver enzymes are common with etretinate, but there have been few reports of acute hepatitis[1,2] or cholestatic jaundice.[3] Acute hepatitis may progress to chronic active hepatitis, despite stopping etretinate therapy[4] but studies of serial liver biopsies from patients receiving long-term etretinate have failed to show any significant chronic liver damage.[5-7] Licensed product information has included reports of hepatic fibrosis, necrosis, and/or cirrhosis.

An overview considered that some form of hepatotoxicity may be seen in up to 20% of patients treated with etretinate and significant liver disease in 1%.[8]

Isotretinoin may also cause mild elevations of liver enzymes and licensed product information states that hepatitis has occurred rarely. There is also a report of fatty liver.[9]

1. Poged EK, Jacobsen PK. Side effects due to RO 10-9359 (Tigason). *Dermatologica* 1982; 164: 395–403.
2. Weiss VC, *et al.* Hepatotoxic reactions in a patient treated with etretinate. *Arch Dermatol* 1984; 120: 104–6.
3. Gavish D, *et al.* Cholestatic jaundice, an unusual side effect of etretinate. *J Am Acad Dermatol* 1985; 13: 669–70.
4. Weiss VC, *et al.* Chronic active hepatitis associated with etretinate therapy. *Br J Dermatol* 1985; 112: 591–7.
5. Glazer SD, *et al.* Ultrastructural survey and tissue analysis of human livers after a 6-month course of etretinate. *J Am Acad Dermatol* 1984; 10: 632–8.
6. Poged E, *et al.* Histologic changes in the liver during etretinate treatment. *J Am Acad Dermatol* 1984; 11: 580–3.
7. Roenigk HH, *et al.* Serial liver biopsies in psoriatic patients receiving long-term etretinate. *Br J Dermatol* 1985; 112: 77–81.
8. Boyd AS. An overview of the retinoids. *Am J Med* 1989; 86: 568–74.
9. Taylor AEM, Mitchison H. Fatty liver following isotretinoin therapy. *Br J Dermatol* 1991; 124: 505–6.

Effects on mental function. Case reports provide evidence of depression, psychotic symptoms, suicide, and suicide attempts occurring as idiosyncratic adverse effects of isotretinoin. However, the high background prevalence of psychiatric illness among adolescents in general, and among patients with acne, are potentially confounding factors. Most retrospective studies have not shown a clear cause and effect mechanism and prospective studies have been limited by sample size and although one large case-crossover study found an association between isotretinoin and depression,[1] the findings were contested.[2] Systematic reviews have found no strong evidence for an association between isotretinoin use and depression or suicidal behaviour, but noted that the evidence was not sufficiently compelling to rule out a weak association,[3,4] although other factors were probably more important.[3] In the absence of better evidence, monitoring for depression and other psychiatric effects has been advised for all patients receiving isotretinoin.[1,5-8]

Two cases of sustained dreaming have also been reported. After 2 to 3 weeks of oral isotretinoin, both patients reported changes in their dreaming pattern with a feeling that they had been 'dreaming all night'. The dreams persisted for 4 to 5 weeks after which they subsided despite continued isotretinoin therapy.[9]

1. Azoulay L, *et al.* Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry* 2008; 69: 526–32.
2. Thakrar BT, Robinson NJ. Isotretinoin and the risk of depression. *J Clin Psychiatry* 2009; 70: 1475.
3. Marqueling AL, Zane LT. Depression and suicidal behavior in acne patients treated with isotretinoin: a systematic review. *Semin Cutan Med Surg* 2005; 24: 92–102.
4. Strahan JE, Raimer S. Isotretinoin and the controversy of psychiatric adverse effects. *Int J Dermatol* 2006; 45: 789–99.
5. Ng CH, Schweitzer I. The association between depression and isotretinoin use in acne. *Aust N Z J Psychiatry* 2003; 37: 78–84.
6. Adverse Drug Reactions Advisory Committee (ADRAC). Acne, isotretinoin and suicidality. *Aust Adverse Drug React Bull* 2005; 24: 10. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0506.htm (accessed 27/09/07)
7. CHM/MHRA. Isotretinoin (Roaccutane): psychiatric adverse reactions. *Current Problems* 2006; 31: 8–9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 27/09/07)
8. Goodfield MJD, *et al.* British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; 162: 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 27/05/10)
9. Gupta MA, Gupta AK. Isotretinoin use and reports of sustained dreaming. *Br J Dermatol* 2001; 144: 919–20.

Effects on the musculoskeletal system. Hyperostotic changes (bone spurs) or calcification of tendons and ligaments, resembling *diffuse idiopathic skeletal hyperostosis* (DISH), have been reported with systemic retinoid therapy.[1,2] DISH-like hyperostotic changes are common in the general population and are associated with ageing; the use of chronic retinoid therapy may increase the risk of developing these changes. Reports have particularly involved patients with keratinisation disorders being treated with large doses of retinoids for prolonged periods, and radiographic changes can be found in most patients after long-term treatment. However, minimal bone changes have also been found in radiographic studies of patients treated with isotretinoin in the dose range usually used to treat acne. Changes were also reported in a study of very low doses of isotretinoin used over 3 years to investigate skin cancer prevention. There have been few reports on the skeletal adverse effects of chronic low-dose etretinate and acitretin and results so far have been equivocal;[2] further studies are needed to clarify any effects. *Premature closure of the epiphyses* in children treated with retinoids has also been described.[1] Again, high doses or prolonged therapy were often used. There is limited evidence to suggest that children might also be at increased risk of slender long bones. There have been rare reports of changes in bone mineral density and *osteoporosis* from retinoid therapy, but there is limited evidence to confirm this association.[1] Ongoing clinical surveillance and periodic radiographic skeletal surveys have been recommended during long-term therapy; symptomatic bone spurs may be treated surgically.[1]

There have also been individual reports of *hypercalciuria*[3] or *hypercalcaemia*[4-6] associated with oral retinoid therapy.

Muscular disorders such as myalgia are not uncommon in patients treated with oral isotretinoin. Reversible myopathy with muscle pain, weakness, and raised creatine kinase concentrations has been described in a few patients treated with isotretinoin,[7] etretinate,[8] and acitretin.[9] Asymptomatic muscle damage has also been found in a study of patients given etretinate for at least a year.[10] Rhabdomyolysis and myoglobinuria have been described in a patient given isotretinoin for acne.[11] Myositis, often affecting the lower limbs, has occurred in a few patients given tretinoin for remission induction in acute promyelocytic leukaemia.[12-15] In one case, cardiac myositis also occurred.[14] Symptoms usually had an onset of 2 to 4 weeks and responded to stopping tretinoin and being treated with a corticosteroid. In a few cases, subsequent courses of tretinoin were given without recurrence of symptoms.[14,15] A review[15] suggested that some cases of myositis might have been associated with the retinoic acid syndrome (see under Tretinoin, p. 1726.2) or Sweet's syndrome (see Effects on the Skin, under Tretinoin, p. 1726.2).

1. DiGiovanna JJ. Isotretinoin effects on bone. *J Am Acad Dermatol* 2001; 45: S176–S182.
2. Halverstam CP, *et al.* Lack of significant skeletal changes after long-term, low-dose retinoid therapy: case report and review of the literature. *J Cutan Med Surg* 2006; 10: 291–9.
3. Wilson DJ, *et al.* Skeletal hyperostosis and extraosseous calcification in patients receiving long-term etretinate (Tigason). *Br J Dermatol* 1988; 119: 597–607.
4. Valentic JP, *et al.* Hypercalcemia associated with oral isotretinoin in the treatment of severe acne. *JAMA* 1983; 250: 1899–1900.
5. Horber FF, *et al.* Impaired renal function and hypercalcaemia associated with etretinate. *Lancet* 1984; ii: 1093.
6. Akiyama H, *et al.* Hypercalcaemia due to all-trans retinoic acid. *Lancet* 1992; 339: 308–9.
7. Hodak E, *et al.* Muscle damage induced by isotretinoin. *BMJ* 1986; 293: 425–6.
8. Hodak E, *et al.* Etretinate-induced skeletal muscle damage. *Br J Dermatol* 1987; 116: 623–6.
9. Lister RK, *et al.* Acitretin-induced myopathy. *Br J Dermatol* 1996; 134: 989–90.
10. David M, *et al.* Electromyographic abnormalities in patients undergoing long-term therapy with etretinate. *J Am Acad Dermatol* 1988; 19: 273–5.
11. Guttman-Yassky E, *et al.* Acute rhabdomyolysis and myoglobinuria associated with isotretinoin treatment. *Int J Dermatol* 2003; 42: 499–500.
12. Miranda N, *et al.* Myositis with tretinoin. *Lancet* 1994; 334: 1096.
13. Martínez-Chamorro C, *et al.* ATRA-induced myositis in induction therapy of acute promyelocytic leukemia. *Haematologica* 2002; 87: ECR08.
14. Fabbiano F, *et al.* All-trans retinoic acid induced cardiac and skeletal myositis in induction therapy of acute promyelocytic leukaemia. *Br J Haematol* 2005; 129: 444–5.
15. Chan KH, *et al.* A case of all-trans retinoic acid-induced myositis in the treatment of acute promyelocytic leukaemia. *Clin Lab Haematol* 2005; 27: 399–401.

Effects on the nervous system. There has been a report[1] of Guillain-Barré syndrome in 2 patients taking oral isotretinoin; both patients required ventilatory support and recovered slowly after treatment with intravenous immunoglobulins. There had been 1 case reported previously to the UK CSM. Intracranial hypertension, causing headaches and papilloedema, can occur with retinoids, including isotretinoin (see Effects on the Eyes, p. 1707.3).

1. Pritchard J, *et al.* Guillain-Barré syndrome seen in users of isotretinoin. *BMJ* 2004; 328: 1537.

Effects on the respiratory system. There have been reports of exercise-induced wheezing,[1] eosinophilic pleural effusion,[2] and worsening asthma[3,4] associated with isotretinoin therapy. The US manufacturers have records of adverse effects on the lung including worsening asthma, recurrent pneumothorax, interstitial fibrosis, and pulmonary granuloma.[5] A study of healthy subjects confirmed that lung function tests could deteriorate after treatment with isotretinoin.[5]

1. Fisher DA. Exercise-induced bronchoconstriction related to isotretinoin therapy. *J Am Acad Dermatol* 1985; 13: 524.
2. Bunker CB, *et al.* Isotretinoin and eosinophilic pleural effusion. *Lancet* 1989; i: 435–6.
3. Sabroe RA, *et al.* Bronchospasm induced by isotretinoin. *BMJ* 1996; 312: 886.
4. Kapur N, *et al.* Exacerbation of asthma by isotretinoin. *Br J Dermatol* 2000; 142: 388–9.
5. Bunker CB, *et al.* Isotretinoin and the lung. *Br J Dermatol* 1991; 125 (suppl 38): 29.

Effects on serum lipids. The oral retinoids induce dose-dependent changes in serum lipids. There can be increases in very-low-density-lipoprotein cholesterol with smaller increases in low-density-lipoprotein cholesterol and reductions in high-density-lipoprotein cholesterol.[1,2] These effects appear to be unrelated to age or sex. They occur early during treatment and are usually reversible within a few weeks of withdrawal. Overall, the effect of isotretinoin is much greater than that of etretinate. Although the total cholesterol and triglyceride concentrations may remain within normal limits, types IIb and IV hyperlipidaemias are not uncommon among patients receiving oral retinoids. A large retrospective study[3] of patients treated with isotretinoin for acne found that of those who had normal concentrations before treatment, there was an increase in triglycerides in 44% and in total cholesterol in 31% of

patients. Pancreatitis may be associated with hypertriglyceridaemia in patients treated with isotretinoin.[4-7]

Retinoids should be used with caution in patients with pre-existing hypertriglyceridaemia or in those at risk of developing hypertriglyceridaemia.[1] Use of fish oil containing eicosapentaenoic acid has been reported to attenuate retinoid-induced increases in serum-cholesterol and serum-triglyceride concentrations.[2,8]

1. Henkin Y, *et al.* Secondary dyslipidemia: inadvertent effects of drugs in clinical practice. *JAMA* 1992; 267: 961–8.
2. Mantel-Teeuwisse AK, *et al.* Drug-induced lipid changes: a review of the unintended effects of some commonly used drugs on serum lipid levels. *Drug Safety* 2001; 24: 443–56.
3. Zane LT, *et al.* A population-based analysis of laboratory abnormalities during isotretinoin therapy for acne vulgaris. *Arch Dermatol* 2006; 142: 1016–22.
4. Flynn WJ, *et al.* Pancreatitis associated with isotretinoin-induced hypertriglyceridemia. *Ann Intern Med* 1987; 107: 63.
5. McCarter TL, Chen YK. Marked hyperlipidemia and pancreatitis associated with isotretinoin therapy. *Am J Gastroenterol* 1992; 87: 1855–8.
6. Jamshidi M, *et al.* Acute pancreatitis secondary to isotretinoin-induced hyperlipidemia. *J Okla State Med Assoc* 2002; 95: 79–80.
7. Greene JP. An adolescent with abdominal pain taking isotretinoin for severe acne. *South Med J* 2006; 99: 992–4.
8. Marsden JR. Effect of dietary fish oil on hyperlipidaemia due to isotretinoin and etretinate. *Hum Toxicol* 1987; 6: 219–22.

Effects on sexual function. Ejaculatory failure has been reported in 3 men to be associated with isotretinoin treatment.[1] A possible mechanism could be an effect on the goblet cells of the seminal vesicles, an effect similar to the general reduction in body secretions which leads to dry mucous membranes.

1. Coleman R, MacDonald D. Effects of isotretinoin on male reproductive system. *Lancet* 1994; 344: 198.

Effects on the skin, hair, and nails. Apart from the more common effects of oral retinoids on the skin and hair (see Adverse Effects, p. 1707.2), there have been isolated reports of various other reactions. Stickiness of the skin, particularly of the palms and soles, has been described with etretinate.[1,2] It has also occurred in a patient using topical tretinoin,[3] but not when he had previously taken a course of oral isotretinoin. Papules and pustules on the palms and soles have also been described with etretinate use.[4] In a series of 5 patients being treated for psoriasis, the lesions appeared 5 to 9 days after starting therapy and cleared spontaneously within a few weeks leaving a desquamation, despite continuing etretinate.

Granulomatous nodules or pyogenic granulomas have been reported with isotretinoin,[5,6] etretinate,[7,8] topical tretinoin,[9,10] and topical tazarotene.[11] Pyoderma gangrenosum has occurred in patients treated with isotretinoin.[12-14] Prurigo-like eruptions have been reported with etretinate.[15] Precipitation or exacerbation of erythroderma has been reported with isotretinoin,[16] etretinate,[17] and acitretin.[18]

Reversible chloasma (melasma) has been reported with isotretinoin.[19]

Acne fulminans is an uncommon complication of acne, developing as a sudden onset of ulcerative crusting acne with fever, weight loss, and musculoskeletal pain. Although isotretinoin may be used to treat this condition,[20] there have been reports of acne fulminans being precipitated by isotretinoin.[21,22] In some cases erythema nodosum has also developed,[23,24] but it has been suggested that this might be a manifestation of acne fulminans rather than an adverse effect of isotretinoin.[24] Erythema nodosum has also occurred in patients given oral tretinoin for remission induction in acute promyelocytic leukaemia. In a series of 4 cases, patients were successfully managed with a 5-day course of oral corticosteroid allowing the tretinoin course to be completed.[25]

There has been a report of fatal toxic epidermal necrolysis associated with etretinate.[26] Reports of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis are also mentioned in the licensed product information for isotretinoin.

For other reports of eruptions associated with vasculitic syndromes, see below. Painful scrotal ulcers and Sweet's syndrome (acute febrile neutrophilic dermatosis) are other reactions that have been reported with oral tretinoin (see p. 1726.2). Skin erosion after wax depilation has been reported in patients receiving retinoids (see Skin Fragility under Precautions, p. 1710.1).

Curling hair has been described in transplant recipients taking isotretinoin and azathioprine.[27] Oral retinoids have been associated with nail fragility, onycholysis,[28] paronychia, and other forms of nail dystrophy.[29,30]

1. Penneys NS, Hernandez D. A sticky problem with etretinate. *N Engl J Med* 1991; 325: 521.
2. Higgins EM, Pembroke AC. Sticky palms—an unusual side-effect of etretinate therapy. *Clin Exp Dermatol* 1993; 18: 389–90.
3. Lockridge J, *et al.* Tretinoin-induced sticky skin: a case report and review of the literature. *Cutis* 1999; 63: 142–4.
4. David M, *et al.* Palmoplantar eruption associated with etretinate therapy. *Acta Derm Venereol (Stockh)* 1986; 66: 87–9.
5. Lane PR, Hogan DJ. Granulomatous lesions appearing during isoretinoin therapy. *Can Med Assoc J* 1984; 130: 550.
6. Türel A, *et al.* A rare side-effect of systemic isotretinoin treatment: pyogenic granuloma. *J Eur Acad Dermatol Venereol* 2003; 17: 609–11.
7. Williamson DM, Greenwood R. Multiple pyogenic granulomata occurring during etretinate therapy. *Br J Dermatol* 1983; 109: 615–17.
8. Kanoh H, *et al.* Granulomatous nodule on vocal cord possibly induced by etretinate therapy. *Br J Dermatol* 2000; 142: 1258–60.
9. MacKenzie-Wood AR, Wood G. Pyogenic granuloma-like lesions in a patient using topical tretinoin. *Australas J Dermatol* 1998; 39: 248–50.
10. Teknetzis A, *et al.* Pyogenic granulomas following topical application of tretinoin. *J Eur Acad Dermatol Venereol* 2004; 18: 337–9.
11. Dawkins MA, *et al.* Pyogenic granuloma-like lesion associated with topical tazarotene therapy. *J Am Acad Dermatol* 2000; 43: 154–5.
12. Hughes BR, Cunliffe WJ. Development of folliculitis and pyoderma gangrenosum in association with abdominal pain in a patient following treatment with isotretinoin. *Br J Dermatol* 1990; 122: 683–7.
13. Gangaram HB, *et al.* Pyoderma gangrenosum following treatment with isotretinoin. *Br J Dermatol* 1997; 136: 636–7.
14. Freiman A, Brassard A. Pyoderma gangrenosum associated with isotretinoin therapy. *J Am Acad Dermatol* 2006; 55 (suppl): S107–S108.
15. Boer J, Smeenk G. Nodular prurigo-like eruptions induced by etretinate. *Br J Dermatol* 1987; 116: 271–4.
16. Wantzin GL, Thomsen K. A new cutaneous side effect of isotretinoin. *J Am Acad Dermatol* 1985; 13: 665.
17. Levin J, Almeyda J. Erythroderma due to etretinate. *Br J Dermatol* 1985; 112: 373.
18. Mahé E, *et al.* Acitretin-induced erythroderma in a psoriatic patient. *J Eur Acad Dermatol Venereol* 2006; 20: 1133–4.
19. Burke H, Carmichael AJ. Reversible melasma associated with isotretinoin. *Br J Dermatol* 1996; 135: 862.
20. Seukeran DC, Cunliffe WJ. The treatment of acne fulminans: a review of 25 cases. *Br J Dermatol* 1999; 141: 307–9.
21. Huston NR, Mules R. Acne fulminans with severe myalgia precipitated by isotretinoin therapy. *N Z Med J* 1985; 36: 821.
22. Choi EH, Bang D. Acne fulminans and 13-cis-retinoic acid. *J Dermatol* 1992; 19: 378–83.
23. Kellett JK, *et al.* Erythema nodosum and circulating immune complexes in acne fulminans after treatment with isotretinoin. *BMJ* 1985; 290: 820.
24. Tan BB, *et al.* Acne fulminans and erythema nodosum during isotretinoin therapy responding to dapsone. *Clin Exp Dermatol* 1997; 22: 26–7.
25. Kuo MC, *et al.* All-trans-retinoic acid-induced erythema nodosum in patients with acute promyelocytic leukemia. *Ann Hematol* 2004; 83: 376–80.
26. McIvor A. Fatal toxic epidermal necrolysis associated with etretinate. *BMJ* 1992; 304: 548.
27. van der Pijl JW, *et al.* Isotretinoin and azathioprine: a synergy that makes hair curl? *Lancet* 1996; 348: 622–3.
28. Önder M, *et al.* Isotretinoin-induced nail fragility and onycholysis. *J Dermatol Treat* 2001; 12: 115–16.
29. Dharmagunawardena B, Charles-Holmes R. Median canaliform dystrophy following isotretinoin therapy. *Br J Dermatol* 1997; 137: 658–9.
30. Yung A, *et al.* Isotretinoin-induced elkonyxis. *Br J Dermatol* 2005; 153: 671–2.

Effects on taste. Almost complete loss of taste has been reported in a patient given oral isotretinoin 600 micrograms/kg daily for 20 weeks.[1] Sense of taste returned about 6 months after isotretinoin was stopped. Up to September 1994 the UK CSM knew of 5 cases of taste changes, including 4 reports of loss of taste.

1. Halpern SM, *et al.* Loss of taste associated with isotretinoin. *Br J Dermatol* 1996; 134: 378.

Overdosage. Apart from vague abdominal discomfort there were no other symptoms or significant abnormalities in a 15-year-old who was treated with gastric lavage 1.5 hours after ingestion of 350 mg of isotretinoin.[1] The authors noted a similar outcome in 2 other cases of isotretinoin overdosage reported in the literature at that time. In a subsequent report, mild headache, skin that was dry and peeling, and cheilitis occurred in a 29-year-old who ingested 900 mg of isotretinoin.[2]

1. Hepburn NC. Deliberate self-poisoning with isotretinoin. *Br J Dermatol* 1990; 122: 840–1.
2. Aubin S, *et al.* Massive isotretinoin intoxication. *Clin Exp Dermatol* 1995; 20: 348–50.

Vasculitic syndromes. The manufacturer of isotretinoin and etretinate has received isolated reports of vasculitis associated with the use of these oral retinoids; Wegener's granulomatosis has also been reported after the use of isotretinoin.[1,2] The precise mechanism underlying these effects is unknown; in some patients there may have been a direct toxic effect as symptoms developed shortly after the start of treatment, in other patients the onset was long-delayed and may have been triggered by the incidental use of antibacterials. Vasculitis, manifesting as fever and skin lesions, has been reported in patients given oral tretinoin for acute promyelocytic leukaemia.[3]

1. Dwyer JM, *et al.* Vasculitis and retinoids. *Lancet* 1989; ii: 494–6.
2. Anonymous. Retinoids and necrotizing vasculitis. *WHO Drug Inf* 1989; 3: 187.
3. Paydas S, *et al.* Vasculitis associated with all trans retinoic acid (ATRA) in a case with acute promyelocytic leukemia. *Leuk Lymphoma* 2003; 44: 547–8.

Precautions

Isotretinoin and other oral retinoids are teratogenic and therefore contra-indicated in pregnant patients. It is advisable for female patients to begin using contraceptive measures 1 month before starting isotretinoin treatment. Pregnancy should be excluded before starting therapy and avoided during treatment and for 1 month after stopping treatment. Patients receiving isotretinoin should not donate blood during, or for 1 month after stopping therapy, because of the potential risk to the fetus of a pregnant transfusion recipient. *Pregnancy or blood donation must be avoided for much longer periods in patients taking acitretin or etretinate.*

Isotretinoin is contra-indicated in patients with hepatic impairment, hyperlipidaemias, and hypervitaminosis A. Renal impairment does not affect the pharmacokinetics of isotretinoin but a lower starting dose has been suggested in severe impairment. It is unknown whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely; isotretinoin use in breast-feeding women is therefore contra-indicated because of the potential for adverse effects in the infant. Isotretinoin should be used with care in patients with a history of depression and patients taking isotretinoin should be monitored for signs of depressive illness.

Liver function and fasting blood lipids should be measured at the start of therapy, after the first month (or every 1 to 2 weeks for the first 2 months for acitretin), and thereafter as appropriate. Blood glucose should be monitored throughout treatment in patients who either have, or are predisposed to, diabetes mellitus. Some recommend routine radiological evaluation in patients receiving long-term therapy (see under Effects on the Musculoskeletal System, p. 1708.2). Patients may have a reduced tolerance to contact lenses.

Excessive exposure to sunlight and UV light should be avoided.

Dizziness, drowsiness, and visual disturbances may occur rarely, and could affect the performance of skilled tasks such as driving.

When applied topically the precautions described under tretinoin (see p. 1726.3) should be considered.

Pregnancy. The problem of prescribing oral retinoids to women of child-bearing potential has been discussed.[1,2] Intra-uterine exposure to isotretinoin has caused spontaneous abortion and a characteristic pattern of fetal malformations involving craniofacial, cardiac, thymic, and CNS structures.[3,4] Some infants have also shown subnormal intelligence and other neuropsychological impairments.[5] The risk of malformation appears to be high at all therapeutic doses of isotretinoin even when the duration of exposure is short.[6] Despite warnings on the use of retinoids during pregnancy and the need for adequate contraception in women of child-bearing potential, and other strict guidelines on their use, intra-uterine exposure to retinoids has still occurred.[7-10]

Isotretinoin has a relatively short half-life and it has been recommended that conception should be avoided for at least one month after the end of treatment.[11] A survey of women who conceived after the use of isotretinoin (64% within one month of stopping treatment) suggested that the incidence of spontaneous abortion or congenital malformations was no greater than in the general population.[12]

Warnings to avoid conception are similar for oral tretinoin (see p. 1726.3). However, patients taking oral retinoids with longer half-lives must avoid conception for much longer periods; at least 2 years (3 years in the USA) is recommended if patients are taking acitretin although the period of time for patients taking etretinate has not been established (see also Pregnancy under Acitretin, p. 1691.3).

Unless otherwise contra-indicated, oral combined contraceptives have been recommended as the contraceptive method of choice for women undergoing retinoid treatment, starting at least 1 month before the retinoid.[13] Use of an additional form of contraception, such as a barrier method, is also recommended.[2,7,11] For further information on the use of hormonal contraceptives with retinoids, see p. 2243.3.

1. Mitchell AA. Oral retinoids: what should the prescriber know about their teratogenic hazards among women of child-bearing potential? *Drug Safety* 1992; 7: 79–85.
2. Chan A, *et al.* Oral retinoids and pregnancy. *Med J Aust* 1996; 165: 164–7.
3. Lammer EJ, *et al.* Retinoic acid embryopathy. *N Engl J Med* 1985; 313: 837–41.
4. Rosa F. Isotretinoin dose and teratogenicity. *Lancet* 1987; ii: 1154.
5. Adams J. High incidence of intellectual deficits in 5-year-old children exposed to isotretinoin 'in utero'. *Teratology* 1990; 41: 614.
6. Dai WS, *et al.* Epidemiology of isotretinoin exposure during pregnancy. *J Am Acad Dermatol* 1992; 26: 599–606.
7. Atanackovic G, Koren G. Fetal exposure to oral isotretinoin: failure to comply with the Pregnancy Prevention Program. *Can Med Assoc J* 1999; 160: 1719–20.
8. CDC. Accutane-exposed pregnancies—California, 1999. *MMWR* 2000; 49: 28–31.
9. Adverse Drug Reactions Advisory Committee (ADRAC). Avoiding fetal abnormalities with isotretinoin. *Aust Adverse Drug React Bull* 2005; 24: 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0502.htm (accessed 27/09/07)
10. Abrams L, *et al.* What is the best approach to reducing birth defects associated with isotretinoin? *PLoS Med* 2006; 3: e483. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0030483 (accessed 23/07/10)
11. Goodfield MJD, *et al.* British Association of Dermatologists. Advice on the safe introduction and continued use of isotretinoin in acne in the UK 2010. *Br J Dermatol* 2010; 162: 1172–9. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Isotretinoin%20Guidelines%202010.pdf (accessed 27/05/10)
12. Dai WS, *et al.* Safety of pregnancy after discontinuation of isotretinoin. *Arch Dermatol* 1989; 125: 362–5.
13. Lehucher Ceyrac D, *et al.* Retinoids and contraception. *Dermatology* 1992; 184: 161–70.

Skin fragility. Wax depilation should be avoided in patients receiving retinoids since they cause increased skin fragility and facial and leg erosions have occurred.[1-3] Licensed UK product information also recommends that wax depilation should be avoided for at least 6 months after isotretinoin treatment because of the risk of epidermal stripping. Aggressive chemical dermabrasion and cutaneous laser treatment should also be avoided for a period of 5 to 6 months after treatment because of the risk of hypertrophic scarring in atypical areas and, more rarely, post-inflammatory hypo- or hyperpigmentation in treated areas.

1. Egido Romo M. Isotretinoin and wax epilation. *Br J Dermatol* 1991; 124: 393.
2. Holmes SC, Thomson J. Isotretinoin and skin fragility. *Br J Dermatol* 1995; 132: 165.
3. Woollons A, Price ML. Roaccutane and wax epilation: a cautionary tale. *Br J Dermatol* 1997; 137: 839–40.

Interactions

Use of isotretinoin with vitamin A (including dietary supplements) should be avoided because of additive toxic effects. Tetracyclines should be avoided as their use with isotretinoin has been associated with the development of benign intracranial hypertension. Skin irritation may be increased if isotretinoin is given with topical keratolytic or exfoliative anti-acne treatments; such use should be avoided.

Antiepileptics. For the effect of isotretinoin on *carbamazepine*, see Dermatological Drugs, p. 517.3.

Hormonal contraceptives. For discussion of the potential interactions of retinoids with oral hormonal contraceptives, and the effect this might have on contraceptive choice during retinoid treatment, see p. 2243.3.

Pharmacokinetics

Isotretinoin is absorbed from the gastrointestinal tract and absorption may be increased by food. Minimal systemic absorption occurs after topical application. Peak plasma concentrations occur 1 to 4 hours after oral doses. Oral bioavailability is low, possibly due to metabolism in the gut wall and first-pass metabolism in the liver. Isotretinoin is highly bound to plasma proteins. It is metabolised in the liver to its major metabolite 4-oxo-isotretinoin; there is also some isomerisation of isotretinoin to tretinoin. Several cytochrome P450 isoenzymes are involved in isotretinoin metabolism, including CYP2C8, CYP2C9, CYP3A4, and CYP2B6. Isotretinoin, tretinoin, and their metabolites undergo enterohepatic recycling. The terminal elimination half-life of isotretinoin is 10 to 20 hours, while that of the 4-oxo metabolite may be up to 50 hours; return to physiological levels of retinoids takes about 2 weeks after stopping therapy. Equal amounts of a dose appear in the faeces, mainly as unchanged drug, and in the urine as metabolites.

Isotretinoin crosses the placenta. It is unknown whether isotretinoin is distributed into breast milk but its lipophilicity makes this likely.

References.

1. Colburn WA, *et al.* Food increases the bioavailability of isotretinoin. *J Clin Pharmacol* 1983; 23: 534–9.
2. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. *Clin Pharmacokinet* 1985; 10: 38–62.
3. Kraft JC, *et al.* Embryonic retinoid concentrations after maternal intake of isotretinoin. *N Engl J Med* 1989; 321: 262.
4. Larsen FG, *et al.* Pharmacokinetics and therapeutic efficacy of retinoids in skin diseases. *Clin Pharmacokinet* 1992; 23: 42–61.
5. Chen C, *et al.* Negligible systemic absorption of topical isotretinoin cream: implications for teratogenicity. *J Clin Pharmacol* 1997; 37: 279–84.
6. Nulman I, *et al.* Steady-state pharmacokinetics of isotretinoin and its 4-oxo metabolite: implications for fetal safety. *J Clin Pharmacol* 1998; 38: 926–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Atlacne; Curacne; Isotrex; Retinide; Roaccutan; Zonatian; ***Austral.***: Accure†; Isohexal†; Isotrex; Oratane; Roaccutane; Rocta; Rocta; ***Austria***: Ciscutan; Lurantal; Roaccutan†; ***Belg.***: Isocural; Isosupra Lidose; Roaccutane; ***Braz.***: Acnil†; Cecnoin; Isofacet; Isotrex; Lurantal; Roacutan; ***Canad.***: Accutane; Clarus; ***Chile***: Acneral; Acnotin; Isdiben; Isocross; Isotrex; Piplex; Roacnetan; ***China***: Ai Si Jie (爱思洁); Isotrex (安泰丝); Tai Er Si (泰尔丝); Teweisi (特维丝); ***Cz.***: Aknenormin; Curacne; Isotretin†; Roaccutane; Stiefel Acne Gel; ***Denm.***: Accutin; Capsoderm†; Isotrex; Tretiosan; ***Fin.***: Roaccutan; ***Fr.***: Contracne; Curacne; Procuta; ***Ger.***: Aknefug Iso; Aknenormin; Isoderm; IsoGalen; Isotret†; Isotrex; ***Gr.***: A-Cnotren; Accuran; Acnogen; Acnotan; Aknesil; Curacne; Derminoin; Flitrion; Inotrin; Isodermal; Isogeril; Isoskin; Isotroin; Lyotret; Noitron; Noroseptan; Novacne; Opridan; Policano; Reducar; Roaccutan; Rocne; Stiefotrex; Trecifan; Tretin; ***Hong Kong***: Acnotin; Isotrex; Reducar; Roaccutane; ***Hung.***: Aknenormin; Isotrex; Roaccutan; Sotret; Tretinak†; ***India***: Acnex; Acno; Acutret; Cutret; Elvac; Iret; Isac; Iso-Aret; Isobest; Isofact; Isoret; Isotane; Isotin; Isotriz; Isotroin; Nextin; ***Indon.***: Isotrex; ***Irl.***: Isotrex; Roaccutane; ***Israel***: Curatane; Isotrex†; Roaccutane; ***Ital.***: Aisoskin; Isoriac; Isotrex; Roaccutan; ***Malaysia***: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Mex.***: Isoface; Isotrex; Neotrex; Oratane; Roaccutan; Sotrexe; Vastionin; ***Mon.***: Roaccutane; ***Neth.***: Curacnet†; Roaccutane; ***Norw.***: Roaccutan†; ***NZ***: Isotane†; Isotrex; Oratane; ***Philipp.***: Acnetrex; Acutrex; Isotrex; Roaccutane; ***Pol.***: Aknenormin; Axotret; Curacne; Isotrex; Izotek; Izotziaja; Roaccutane†; Tretinex; ***Port.***: Isdiben; Isoprotil; Isotrex; Orotrex; ***Rus.***: Retasol (Ретасол); Retinoic Ointment (Ретиноевая Мазь); Roaccutane (Роаккутан); ***S.Afr.***: Acnetane; Isotrex; Oratane; Roaccutane; ***Singapore***: Acnotin; Isotrex; Nimegen; Oratane; Roaccutane; ***Spain***: Acnemin; Dercutane; Farmacne; Flexresan; Isdiben; Isoacne; Isotrex; Mayesta; Roacutan†; ***Switz.***: Curakne; Liderma†; Roaccutane; Tretinac; ***Thai.***: A-Cnotren; Acnotin; Isotane; Isotrex; Proacne; Roaccutane; Sotret; Tinoin; ***Turk.***: Acretin; Aknetrent; Roaccutane; Zoretanin; ***UK***: Isotrex; Roaccutane; ***Ukr.***: Acnetin (Акнетин); Roaccutane (Роаккутан); ***USA***: Absorica; Accutane†; Amnesteem; Claravis; Myorisan; Sotret; Zenatane; ***Venez.***: Cutiderm; Isoface; Roaccutan.

Multi-ingredient Preparations. ***Austria***: Isotrex; Isotrexin; ***Braz.***: Isotrexin; Isotrexol; ***Cz.***: Isotrexin; ***Fr.***: Antibiotrex; ***Ger.***: Isotrexin; ***Hung.***: Isotrexin; ***Irl.***: Isotrexin; ***Ital.***: Isotrexin; ***Pol.***: Isotrexin; ***Port.***: Isotrexin; ***Rus.***: Isotrexin (Изотрексин); ***Singapore***: Isotrexin; ***Spain***: Isotrex Eritromicina; ***Thai.***: Isotrexin; ***Turk.***: Isotrexin; ***UK***: Isotrexin; ***Ukr.***: Isotrexin (Изотрексин).

Pharmacopoeial Preparations
BP 2014: Isotretinoin Capsules; Isotretinoin Gel;
USP 36: Isotretinoin Capsules.

Keluamid

Keluamida; Келуамид.

Profile

Keluamid has keratolytic properties and has been used in topical preparations for the treatment of seborrhoeic dermatitis and other scaling skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kelual; ***Fr.***: Kelual.

Multi-ingredient Preparations. ***Arg.***: Kelual Zinc; ***Fr.***: Kelual DS; Kelual DS; Kelual Zinc†; Kertyol-S†.

Kinetin

6-Furfurylaminopurine; N^6-Furfuryladenine; Кинетин.
$C_{10}H_9N_5O$=215.2
CAS — 525-79-1.
UNII — P39Y9652YJ.

NOTE. The name kinetin has also been used as a proprietary name for hyaluronidase (p. 2527.2).

Profile

Kinetin is a plant growth hormone that has been promoted in products for the management of photodamaged skin and hyperpigmentation but good evidence of efficacy appears to be lacking.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Braz.***: Kinerase; ***Hong Kong***: Kinerase; ***Mex.***: Kinerase; ***Singapore***: Kinerase; ***USA***: Kinerase.

Multi-ingredient Preparations. ***Philipp.***: Kinerase.

Kojic Acid

Kójico, ácido; Койевая Кислота.
5-Hydroxy-2-hydroxymethyl-4-pyrone.
$C_6H_6O_4$=142.1
CAS — 501-30-4.
UNII — 6K23F1TT52.

Profile

Kojic acid is reported to inhibit melanin production and is used in topical preparations for the treatment of hyperpigmentation disorders (p. 1687.2). Kojic acid is also used as a food additive.

References.

1. Lim JT. Treatment of melasma using kojic acid in a gel containing hydroquinone and glycolic acid. *Dermatol Surg* 1999; 25: 282–4.
2. Bentley R. From miso, saké and shoyu to cosmetics: a century of science for kojic acid. *Nat Prod Rep* 2006; 23: 1046–62.
3. García-Gavín J, *et al.* Pigmented contact dermatitis due to kojic acid: a paradoxical side effect of a skin lightener. *Contact Dermatitis* 2010; 62: 63–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Chile***: Unitone 4.

Multi-ingredient Preparations. ***Arg.***: Cellskinlab Phyto Spot; Melasoft; Neoquin; ***Braz.***: Melani-D Maos; ***Chile***: Melani-D; NeoStrata; Phyto Spot; Recover Oi; ***India***: Biolite; Carofit; Clearz; Demelan; E-Cate; Glyaha-KOJ; KC-Lite; ***Indon.***: Hidrogel†; ***Ital.***: Brunex; ***Mex.***: Nova Derm Facial Lightening; ***Port.***: Despigmentante†; ***Singapore***: Disco.

Liarozole *(BAN, rINN)*

Liarozol; Liarozolum; Лиарозол.
(±)-5-(*m*-Chloro-α-imidazol-1-ylbenzyl)benzimidazole.
$C_{17}H_{13}ClN_4$=308.8
CAS — 115575-11-6; 145858-51-1.
UNII — K0Q29TGV9Y.

Liarozole Fumarate *(BANM, USAN, rINNM)*

Fumarato de liarozol; Liarozole, Fumarate de; Liarozoli Fumaras; R-85246; Лиарозола Фумарат.
$2C_{17}H_{13}ClN_4.3C_4H_4O_4$=965.8
CAS — 145858-52-2.
UNII — 91W7VLK7J3.

Liarozole Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de liarozol; Liarozole, Chlorhydrate de; Liarozoli Hydrochloridum; R-75251; Лиарозола Гидрохлорид.
$C_{17}H_{13}ClN_4$, HCl=345.2
CAS — 145858-50-0.
UNII — 29T7S2IB97.

Profile

Liarozole, an imidazole analogue, increases plasma and cutaneous retinoic acid concentrations through inhibition of cytochrome P450 isoenzymes involved in retinoic acid catabolism. It is under investigation for the management of ichthyoses and psoriasis.

References.

1. Bhushan M, *et al.* Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2001; 145: 546–53.
2. Lucker GPH, *et al.* Topical liarozole in ichthyosis: a double-blind, left-right comparative study followed by a long-term open maintenance study. *Br J Dermatol* 2005; 152: 566–9.
3. Verfaille CJ, *et al.* Oral liarozole vs. acitretin in the treatment of ichthyosis: a phase II/III multicentre, double-blind, randomized, active-controlled study. *Br J Dermatol* 2007; 156: 965–73.

Lisadimate *(USAN, rINN)*

Glyceryl Aminobenzoate; Glyceryl PABA; Lisadimato; Lisadimatum; Лизадимат.
Glyceryl 1-(4-aminobenzoate).
$C_{10}H_{13}NO_4$=211.2
CAS — 136-44-7.
UNII — A886B5N5IM.

Profile

Lisadimate, a substituted aminobenzoate, is a sunscreen (see p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***India***: Brite; ***USA***: Total Eclipse.

Lithium Succinate

Litio, succinato de; Лития Сукцинат.
$C_4H_6O_4.xLi$
CAS — 16090-09-8.
ATC — D11AX04.
ATC Vet — QD11AX04.
UNII — MD64P82Y28.

Profile

Lithium succinate is reported to have anti-inflammatory properties and is used as an 8% cream or ointment, usually with zinc sulfate. It is applied twice daily initially in the treatment of seborrhoeic dermatitis (p. 1689.1). It should be used with caution in patients with psoriasis as it may exacerbate their condition.

References.
1. Gould DJ, *et al.* A double-blind, placebo-controlled, multicenter trial of lithium succinate ointment in the treatment of seborrheic dermatitis. *J Am Acad Dermatol* 1992; **26**: 452–7.
2. Cuelenaere C, *et al.* Use of topical lithium succinate in the treatment of seborrhoeic dermatitis. *Dermatology* 1992; **184**: 194–7.
3. Langtry JA, *et al.* Topical lithium succinate ointment (Efalith) in the treatment of AIDS-related seborrhoeic dermatitis. *Clin Exp Dermatol* 1997; **22**: 216–19.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Efalith; *Ger.*: Efadermin; *Irl.*: Efalith†; *Switz.*: Efalith.

Maggots

Larvas; Sterile Larvae; Личинки.

Profile

Maggots used in wound management are the live sterile larvae of *Lucilia sericata*, the common greenbottle fly. Larval therapy (sometimes called biosurgery) may be used for debridement of infected or necrotic wounds (p. 1690.1), including diabetic foot ulcers. Maggots produce a mixture of proteolytic enzymes that breaks down the necrotic tissue while leaving the healthy tissue unharmed, and kill or prevent the growth of micro-organisms, particularly Gram-positive bacteria. The movement of the maggots also appears to stimulate the growth of granulation tissue.

The maggots are applied to the surface of the wound and kept in place with dressings for up to 3 days. They are removed with the dressing, and the wound is irrigated with sodium chloride solution; any remaining maggots are removed with forceps.

Maggots should not be applied to wounds that have a tendency to bleed easily, or that communicate with a body cavity or any internal organ. Pain has been reported with larval therapy and some patients may require analgesics.

References.
1. Courtenay M, *et al.* Larva therapy in wound management. *J R Soc Med* 2000; **93**: 72–4.
2. Jukema GN, *et al.* Amputation-sparing treatment by nature: "surgical" maggots revisited. *Clin Infect Dis* 2002; **35**: 1566–71.
3. Sherman RA, Shimoda KJ. Presurgical maggot debridement of soft tissue wounds is associated with decreased rates of postoperative infection. *Clin Infect Dis* 2004; **39**: 1067–70.
4. Armstrong DG, *et al.* Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc* 2005; **95**: 254–7.
5. Steenvoorde P, *et al.* Maggot debridement therapy: free-range or contained? An in-vivo study. *Adv Skin Wound Care* 2005; **18**: 430–5.
6. Dumville JC, *et al.* Larval therapy for leg ulcers (VenUS II): randomised controlled trial. Abridged version: *BMJ* 2009; **338**: 1047–50. Full version: http://www.bmj.com/cgi/reprint/338/mar19_2/b773 (accessed 16/03/10)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: LarvE.

Melanin

Меланин.

Profile

Melanin is a group of natural pigments found in many plants and animals; they are present in human skin and hair. Natural and synthetic forms of melanin have been used in sunscreen preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Fotobloc.

Multi-ingredient Preparations. *Arg.*: Fotocrem Ultra; Melablock; *Chile*: ProZone Face†; ProZone Gel; *Mex.*: ProZone Baby; ProZone Body; ProZone Face; ProZone Gel; ProZone Ultra Fluido; ProZone Ultra.

Mequinol *(USAN, rINN)*

BMS-181,158; Éter metílico de la hidroxiquinona; *p*-Guaiacol; 4-HA; 4-Hidroxianisol; HQMME; Hydroquinone Monomethyl Ether; *p*-Hydroxyanisole; Hydroxyquinone Methyl Ether; Mequinol; Mequinolum; Metoxifenol; *p*-Metoxifenol; Меквинол.

4-Methoxyphenol.

$C_7H_8O_2$=124.1

CAS — 150-76-5.

ATC — D11AX06.

ATC Vet — QD11AX06.

UNII — 6HT8U7K3AM.

Profile

Mequinol is used similarly to hydroquinone (p. 1705.1), in concentrations of up to 20%, in the treatment of hyperpigmentation (see Pigmentation Disorders, p. 1687.2). A preparation containing mequinol 2% with tretinoin 0.01% is used for the treatment of solar lentigines (liver spots).

Adverse effects. A report of severe reversible irregular hypopigmentation of the hands, arms, neck, and legs in a West Indian woman who applied a bleaching wax containing mequinol for 2 to 3 months to lighten the colour of her skin.[1]

1. Boyle J, Kennedy CTC. British cosmetic regulations inadequate. *BMJ* 1984; **288**: 1998–9.

Pigmentation disorders. References.

1. Fleischer AB, *et al.* The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42**: 459–67.
2. Njoo MD, *et al.* Depigmentation therapy in vitiligo universalis with topical 4-methoxyphenol and the Q-switched ruby laser. *J Am Acad Dermatol* 2000; **42**: 760–9.
3. Ortonne JP, *et al.* Safety and efficacy of combined use of 4-hydroxyanisole (mequinol) 2%/tretinoin 0.01% solution and sunscreen in solar lentigines. *Cutis* 2004; **74**: 261–4.
4. Jarratt M. Mequinol 2%/tretinoin 0.01% solution: an effective and safe alternative to hydroquinone 3% in the treatment of solar lentigines. *Cutis* 2004; **74**: 319–22.
5. Draelos ZD. The combination of 2% 4-hydroxyanisole (mequinol) and 0.01% tretinoin effectively improves the appearance of solar lentigines in ethnic groups. *J Cosmet Dermatol* 2006; **5**: 239–44.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Braz.*: Leucodin; *Fr.*: Any; Clairodermyl; Creme des 3 Fleurs d'Orient†; Leucodinine B; *Gr.*: Leucodinine-M; *Spain*: Novo-Dermoquinona.

Multi-ingredient Preparations. *Canad.*: Solage; *USA*: Solage†.

Meradimate *(USAN, rINN)*

Menthyl *O*-Aminobenzoate; Menthyl Anthranilate; Méradimate; Meradimato; Meradimatum; Мерадимат.

5-Methyl-2-(1-methylethyl)-cyclohexyl 2-aminobenzoate.

$C_{17}H_{25}NO_2$=275.4

CAS — 134-09-8.

UNII — J9QGD60OUZ.

NOTE. Do not confuse with methyl anthranilate (p. 1714.2). Neo-Heliopan MA is a trade name that has been used for meradimate.

Pharmacopoeias. In *US*.

USP 36: (Meradimate). Store in airtight containers.

Profile

Meradimate is used as a sunscreen (p. 1681.3). It is effective against UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Fotocrem Ultra; *Austral.*: Blistex Ultra Lip Balm; *Canad.*: Blistex Ultra Protection Lip Balm; Exact Lip Balm Year-Round Protection; Kids Sunscreen; Lip Conditioner Lip Balm; Marcelle Essentials; Marcelle Multi-Defense; Spray-on Sunscreen; Spray-on Sunscreen; Watkins Aloe Vera Botanical Lip Balm; Zoom Protective Lip Cream; *Chile*: Proteccion Ultra; *USA*: A-Fil; Blistex Ultra Protection; Catrix Correction; Hawaiian Tropic Baby Faces; Hawaiian Tropic Protective Tanning Dry; Hawaiian Tropic; Hawaiian Tropic; Hawaiian Tropic; Hawaiian Tropic; Herpecin-L; Lip Tone; Neutrogena; Neutrogena; Neutrogena.

Ammoniated Mercury

Aminomercuric Chloride; Hydrargyri Aminochloridum; Hydrargyrum Amidochloratum; Hydrargyrum Ammoniatum; Hydrargyrum Praecipitatum Album; Mercuric Amidochloride; Mercuric Ammonium Chloride; Mercurio amoniacal; Mercury Amide Chloride; Mercury Aminochloride; Precipitado blanco (de mercurio); White Precipitate; Хлористый Меркураммоний.

NH_2HgCl=252.1

CAS — 10124-48-8.

ATC — D08AK01.

ATC Vet — QD08AK01.

UNII — JD546Z56EG.

NOTE. 'White Precipitate' has also been used as a name for Precipitated Mercurous Chloride.

Pharmacopoeias. In *US*.

USP 36: (Ammoniated Mercury). A white amorphous powder or pulverulent pieces; odourless. It is stable in air, but darkens on exposure to light. Insoluble in water and in alcohol; readily soluble in warm hydrochloric, nitric, and acetic acids. Protect from light.

Profile

Ammoniated mercury was formerly used topically in the treatment of skin infections and psoriasis but the use of such mercurial preparations is generally deprecated. Frequent or prolonged application to large areas or to broken skin or mucous membranes can cause mercury poisoning (see p. 2556.1) and use on infants has produced acrodynia (pink disease). Ammoniated mercury is also a potent sensitiser and can produce allergic reactions.

Homoeopathy

Ammoniated mercury has been used in homoeopathic medicines under the following names: Mercurius praecipitatus albus; Merc praecip alb.

Effects on the kidneys. Of 60 patients who were found to have nephrotic syndrome, 32 had used skin-lightening creams containing 5 to 10% of ammoniated mercury.[1] Concentrations of mercury in the urine of these patients were up to 250 nanograms/mL compared with a usual upper limit of 80 nanograms/mL. Of 26 patients followed up for up to 2 years, 13 had no remission or response to treatment; 6 of these had used skin lighteners.

1. Barr RD, *et al.* Nephrotic syndrome in adult Africans in Nairobi. *BMJ* 1972; **2**: 131–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Cz.*: Homeogene 9; Homeovox.

Mesulphen *(BAN)*

Dimethyldiphenylene Disulphide; Dimethylthianthrene; Mesulfeeni; Mesulfen (pINN); Mesulfen; Mésulfène; Mesulfeno; Mesulfenum; Месульфен.

It consists mainly of 2,7-dimethylthianthrene.

$C_{14}H_{12}S_2$=244.4

CAS — 135-58-0.

ATC — D10AB05; P03AA03.

ATC Vet — QD10AB05; QP53AA01.

UNII — EG6V6W7WDD.

Pharmacopoeias. *Jpn* includes thianthol, a mixture of 2,7-dimethylthianthrene and ditolyl disulfide.

Profile

Mesulphen has been used as a parasiticide and antipruritic in a range of skin disorders including acne, scabies, and seborrhoea. Sensitivity to mesulphen has occasionally been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Soufrol.

Methoxsalen *(BAN)*

Ammoidin; Amoidina; Methoxalenum; 8-Methoxypsoralen; Metoksaleeni; Metoksalen; Metoxalen; Metoxaleno; Metoxipsoraleno; 8-MOP; Xanthotoxin; Xantotoxina; Метоксален.

9-Methoxyfuro[3,2-*g*]chromen-7-one; 9-Methoxy-7*H*-furo[3,2-*g*][1]benzopyran-7-one.

$C_{12}H_8O_4$=216.2

CAS — 298-81-7.

ATC — D05AD02; D05BA02.

ATC Vet — QD05AD02; QD05BA02.

UNII — U4VJ29L7BQ.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Methoxsalen). White to cream-coloured, odourless, fluffy, needle-like crystals. Practically insoluble in water; sparingly soluble in boiling water and in ether; soluble in boiling alcohol, in acetone, in acetic acid, in propylene glycol, and in benzene; freely soluble in chloroform. Protect from light.

Uses and Administration

Methoxsalen, a psoralen, is a constituent of the seeds of *Ammi majus* and the roots of *Heracleum candicans*. It is a photosensitiser that markedly increases skin reactivity to long-wavelength ultraviolet radiation (320 to 400 nm), an effect used in photochemotherapy or PUVA [psoralen (P) and high-intensity long-wavelength UVA irradiation]. In the presence of UVA methoxsalen bonds with DNA, inhibiting DNA synthesis and cell division, and can lead to cell injury. Recovery from the cell injury may be followed by increased melanisation of the epidermis and thickening

of the stratum corneum. Methoxsalen may also increase pigmentation by an action on melanocytes.

PUVA is used to treat idiopathic vitiligo and severe, recalcitrant, disabling psoriasis not adequately responsive to conventional topical therapy. It may also be useful in selected cases of atopic eczema and polymorphic light eruptions and may be used in T-cell lymphomas such as mycosis fungoides.

Methoxsalen is given orally or applied topically in PUVA regimens. *Differing oral dosage forms of methoxsalen may have significantly varying bioavailabilities and times to onset of photosensitisation.* The UVA exposure dose should generally be based on prior measurement of the minimal phototoxic dose although it can be calculated with regard to the skin type of the patient if phototoxic dose testing cannot be carried out.

- To repigment **vitiliginous** areas, methoxsalen is given in a dose of 20 mg or up to 600 micrograms/kg *orally* 2 to 4 hours before measured periods of exposure to UVA, depending on the preparation. Treatment is usually given twice a week or on alternate days, but always at least 48 hours apart.
- Methoxsalen may also be applied *topically* to repigment small, well-defined vitiliginous lesions. Preparations containing up to 1% have been used but dilution to 0.1 or 0.01% may be necessary to avoid adverse cutaneous effects. The surrounding skin should be protected by an opaque sunscreen. Some suggest that the treated area should be exposed to UVA soon after application while others recommend waiting up to 2 hours. After exposure the lesions should be washed and protected from light; protection may be necessary for up to 48 hours or longer. Treatment is repeated usually once weekly. Significant repigmentation may not appear until after 6 to 9 months of treatment.
- For the treatment of **psoriasis** a dose of up to about 600 micrograms/kg *orally* is given 1.5 to 3 hours before UVA, depending on the preparation. Treatment is usually given twice a week although increased frequencies, but with at least 48-hour intervals between doses, have been suggested. If there is no response or only minimal response after the fifteenth PUVA treatment some suggest that the dosage may be increased by 10 mg and that this higher dose be used for the remainder of the course of treatment.
- Methoxsalen may also be used *topically* with UVA exposure for the treatment of psoriasis. For direct application to affected areas of skin a preparation containing about 0.15% (or diluted to 0.015% if necessary to avoid adverse cutaneous effects) is applied 15 minutes before UVA exposure. Alternatively the patient may take a whole body bath for 15 minutes in a methoxsalen solution, followed immediately by UVA exposure. UK guidelines (see also Skin Disorders, below) suggest a typical concentration of methoxsalen 2.6 mg/litre for such solutions although higher concentrations (up to about 3.7 mg/litre) have been used. Hand and foot soaks may be used to treat only those affected areas; a solution containing methoxsalen 3 mg/litre may be used with the affected areas immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. Baths or soaks are generally given twice a week.

Psoralen itself has also been used.

Administration. The dose of methoxsalen is usually calculated on the basis of body-weight. This method of dose calculation produces a considerable difference between the doses received by heavy and light patients. A study in 41 patients with psoriasis[1] suggested that using methoxsalen 25 mg/m^2 gave more consistent plasma concentrations and may reduce the potential for burning in heavy patients and prevent underdosing in light patients undergoing PUVA therapy.

1. Sakuntabhai A, *et al.* Calculation of 8-methoxypsoralen dose according to body surface area in PUVA treatment. *Br J Dermatol* 1995; 133: 919–23.

PUVA. PUVA combines psoralens with UVA irradiation. The psoralens may be given directly to the patient, either orally or topically, and the patient is then exposed to UVA. In extracorporeal PUVA (extracorporeal photochemotherapy; photopheresis), an oral dose of a psoralen is given, after which the patient's leucocytes are isolated, exposed to UVA extracorporeally, and then reinfused. In another method of extracorporeal photopheresis methoxsalen is added directly to leucocytes that have already been removed from the patient. The mixture is then treated with UVA after which it is returned to the patient; the total dose of methoxsalen used by this method is lower than that used orally. PUVA has been used in many disorders including skin disorders, mycosis fungoides, and organ and tissue transplant rejection (below).

MYCOSIS FUNGOIDES. PUVA therapy is used in the treatment of the manifestations of cutaneous mycosis fungoides and Sézary syndrome, two forms of cutaneous T-cell lymphoma (see p. 698.3). Extracorporeal PUVA therapy (photopheresis; see above) has also been used,[1-6] particularly for disease with erythrodermic features. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests a usual treatment cycle of 2 consecutive days, which is repeated every 2 to 4 weeks. More frequent treatment may be given to symptomatic patients and those with a high peripheral blood tumour burden. Response is assessed every 3 months and then, when complete or maximal response has occurred, treatment is tapered to every 6 to 12 weeks before stopping. Relapse may be treated with the same schedule. After the first 3 months of therapy, treatment should generally be continued for a further 3 months in patients with stable disease (no response). However, consideration should be given to stopping treatment, or using combination therapy (photopheresis with interferon alfa and/or bexarotene), if there is disease progression. At 6 months and beyond, treatment should be stopped, or combination therapy considered, in patients with stable or progressive disease, but for those already receiving combination therapy, photopheresis should be stopped.

1. Duvic M, *et al.* Photopheresis therapy for cutaneous T-cell lymphoma. *J Am Acad Dermatol* 1996; 35: 573–9.
2. Zic JA, *et al.* Long-term follow-up of patients with cutaneous T-cell lymphoma treated with extracorporeal photochemotherapy. *J Am Acad Dermatol* 1996; 35: 935–45.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; 3: 50–62.
4. Rubegni P, *et al.* Extracorporeal photochemotherapy in long-term treatment of early stage cutaneous T-cell lymphoma. *Br J Dermatol* 2000; 143: 894–6.
5. Zic JA. The treatment of cutaneous T-cell lymphoma with photopheresis. *Dermatol Ther* 2003; 16: 337–46.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; 154: 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; 158: 659–78.

ORGAN AND TISSUE TRANSPLANTATION. PUVA[1,2] and extracorporeal PUVA therapy[3-6] (photopheresis; see above) have been tried in both acute and chronic graft-versus-host disease (GVHD) that is unresponsive to usual treatment (see Haematopoietic Stem Cell Transplantation, p. 1933.1). As well as improvements in GVHD, particularly cutaneous manifestations, PUVA therapies have enabled the doses of corticosteroids and other immunosuppressants to be reduced. The Photopheresis Expert Group[7] (from the UK and Scandinavia) suggests, for chronic GVHD, a usual treatment cycle of 2 consecutive days, repeated every 2 weeks. Response is assessed after 3 months and treatment reduced to once every 4 weeks if there has been a complete or partial response. Treatment is then re-assessed every 3 months and tapered or stopped when a complete or maximal response has occurred. It should be stopped if there is no response or disease progression.

Photopheresis has also been tried in treating rejection of solid organ transplants,[3,6,8] particularly after heart transplantation (p. 1934.2). It also showed promise in a study[9] of the prevention of heart transplant rejection.

1. Bonanomi S, *et al.* Bath PUVA therapy in pediatric patients with drug-resistant cutaneous graft-versus-host disease. *Bone Marrow Transplant* 2001; 28: 631–2.
2. Furlong T, *et al.* Psoralen and ultraviolet A irradiation (PUVA) as therapy for steroid-resistant cutaneous acute graft-versus-host disease. *Biol Blood Marrow Transplant* 2002; 8: 206–12.
3. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; 3: 50–62.
4. Foss FM, *et al.* Extracorporeal photopheresis in chronic graft-versus-host disease. *Bone Marrow Transplant* 2002; 29: 719–25.
5. Kanold J, *et al.* Extracorporeal photochemotherapy for graft versus host disease in pediatric patients. *Transfus Apheresis Sci* 2003; 28: 71–80.
6. McKenna KE, *et al.* Evidence-based practice of photopheresis 1987–2001: a report of a workshop of the British Photodermatology Group and the U.K. Skin Lymphoma Group. *Br J Dermatol* 2006; 154: 7–20.
7. Scarisbrick JJ, *et al.* Photopheresis Expert Group. U.K. consensus statement on the use of extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease. *Br J Dermatol* 2008; 158: 659–78.
8. Dall'Amico R, Murer L. Extracorporeal photochemotherapy: a new therapeutic approach for allograft rejection. *Transfus Apheresis Sci* 2002; 26: 197–204.
9. Barr ML, *et al.* Photopheresis for the prevention of rejection in cardiac transplantation. *N Engl J Med* 1998; 339: 1744–51.

SKIN DISORDERS. PUVA has been used in many skin disorders and guidelines have been published by the British Photodermatology Group,[1,2] which are summarised as follows:

- Indications for PUVA in chronic plaque **psoriasis** include severe extensive psoriasis unresponsive to conventional topical therapies, relapse within 3 to 6 months of successful topical treatment, or patient refusal of topical treatment if UVB phototherapy has failed (see p. 1688.1 for a discussion of the various treatments of psoriasis). Initial UVA exposure should preferably be determined on the basis of prior measurement of the minimal phototoxic dose rather than on the skin type. Increases in UVA irradiation are then calculated as a percentage of previous doses.

  Methoxsalen in an oral dose of 600 micrograms/kg given 2 hours before UVA exposure is the widely accepted standard regimen. Alternatively, 5-methoxypsoralen 1.2 mg/kg, again 2 hours before UVA exposure, can be given and appears to be almost free of the adverse reactions such as nausea, pruritus, and erythema induced by methoxsalen. However, until the clinical efficacy of 5-methoxypsoralen has been clearly shown, methoxsalen should remain the psoralen of choice for most clinical situations.

  Alternatives to oral PUVA are baths or soaks using methoxsalen or trioxysalen. For whole body bathing a concentration of methoxsalen 2.6 mg/litre is typically utilised with the patient bathing for 15 minutes followed by immediate exposure to UVA. For hand and foot soaks a concentration of methoxsalen 3 mg/litre is used with the affected area immersed for 15 minutes followed by a delay of 30 minutes before UVA exposure. For trioxysalen a concentration of about 330 micrograms/litre is used for a 15-minute whole body bath or hand and foot soak followed by immediate UVA exposure for whole body therapy, or a 30 minute delay before hand and foot UVA exposure. Whole body baths or hand and foot soaks are given twice each week.

  Methoxsalen may also be applied topically to the affected areas. A concentration of about 0.15% (or 0.015% if erythema occurs) is used in an emulsion, or 0.005% in an aqueous gel, and applied 15 minutes before UVA exposure.

  PUVA treatment should be stopped as soon as disease clearance is achieved; maintenance PUVA should be avoided to minimise cumulative UVA exposure, but may be considered if there is rapid relapse. A combination of PUVA with acitretin (300 to 700 micrograms/kg orally) or etretinate (0.5 to 1 mg/kg orally) may be considered in patients who have reached 50 treatment sessions or relapsed within 6 months of PUVA. PUVA and methotrexate are also effective for severe psoriasis but should be reserved for such cases because of the possible increased risk of skin cancer
- Use of oral PUVA twice weekly with methoxsalen 600 micrograms/kg or 5-methoxypsoralen 1.2 mg/kg has been effective in many patients with **vitiligo** (see Pigmentation Disorders, p. 1687.2). If patches are well demarcated topical application of methoxsalen 0.15% may be preferable
- In **mycosis fungoides** PUVA is an effective symptomatic treatment for early disease and a useful adjunct for late-stage disease but optimal regimens have not been established (see above)
- PUVA is effective for atopic **eczema** (p. 1684.1) but clearance is less certain than for psoriasis, twice the number of treatments may be needed, and relapse is more frequent. It should therefore be reserved for severe disease unresponsive to conventional treatments. Optimal regimens have not been established
- In **polymorphic light eruptions** (see Photosensitivity Disorders, p. 1686.2) PUVA is effective in up to 90% of patients but is only indicated in those who are frequently or severely affected despite the regular use of high-protection broad-spectrum sunscreens. Several arbitrary regimens are in use
- Variable results have also been reported in a variety of other disorders but data has been insufficient to establish precise guidelines. Such disorders include actinic prurigo, alopecia areata, aquagenic pruritus, chronic actinic dermatitis, granuloma annulare, lichen planus, nodular prurigo, pityriasis lichenoides, localised scleroderma, solar urticaria, and urticaria pigmentosa. In most cases relapse occurs in the absence of maintenance therapy and PUVA should usually only be tried as a last resort.

Extracorporeal PUVA has been tried in patients with severe epidermolysis bullosa acquisita,[3,4] lichen planus,[5] and scleroderma.[6,7]

1. British Photodermatology Group. British Photodermatology Group guidelines for PUVA. *Br J Dermatol* 1994; 130: 246–55.
2. Halpern SM, *et al.* Guidelines for topical PUVA: a report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2000; 142: 22–31. Also available at: http://www.bad.org.uk/Portals/_Bad/Guidelines/Clinical%20Guidelines/Topical%20PUVA%20Therapy.pdf (accessed 23/07/10)
3. Miller JL, *et al.* Remission of severe epidermolysis bullosa acquisita induced by extracorporeal photochemotherapy. *Br J Dermatol* 1995; 133: 467–71.
4. Gordon KB, *et al.* Treatment of refractory epidermolysis bullosa acquisita with extracorporeal photochemotherapy. *Br J Dermatol* 1997; 136: 415–20.
5. Guyot AD, *et al.* Treatment of refractory erosive oral lichen planus with extracorporeal photochemotherapy: 12 cases. *Br J Dermatol* 2007; 156: 553–6.
6. Zic JA, *et al.* The North American experience with photopheresis. *Ther Apher* 1999; 3: 50–62.
7. Knobler RM, *et al.* A randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. *J Am Acad Dermatol* 2006; 54: 793–9.

Adverse Effects

Methoxsalen given orally commonly causes nausea and less frequently mental effects including insomnia, nervousness, and depression.

Photochemotherapy or PUVA (see under Uses and Administration, p. 1712.1) may cause pruritus and mild transient erythema. Other effects include oedema, dizziness, headache, vesiculation, bulla formation, acneform eruption, and severe skin pain. Overexposure to sunlight or UVA radiation may produce severe burns in patients being treated with psoralens. Hypertrichosis, pigmentation alterations of skin or nails, and onycholysis, have also been reported. PUVA can produce premature ageing of the skin, and may be associated with an increased risk of malignant cutaneous neoplasms.

Carcinogenicity. See under Effects on the Skin, below.

There has been concern about a possible increased risk of noncutaneous malignancies associated with PUVA. However, a long-term study of 1380 patients followed for 20 years reported no overall increase in solid malignancies, lymphoma, or leukaemia.[1]

1. Stern RS, Väkevä LH. PUVA Follow-up Study. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; 108: 897–900.

Effects on the eyes. Free methoxsalen has been detected in the lens of the eye for at least 12 hours after oral doses.[1] It may become integrated into the structure of the lens if there is exposure to UV light, promoting cataract formation in patients who fail to wear suitable eye protection for 12 to 24 hours after methoxsalen ingestion.[2] However, provided that eye protection is used there appears to be no significant dose-dependent increase in the risk of cataract formation,[3] although a higher risk of developing nuclear sclerosis and posterior subcapsular opacities has been noted in patients who have received more than 100 treatments.[4] Other ocular effects include dose-related transient visual-field defects reported in 3 patients receiving PUVA therapy.[5] Psoralens may also increase the sensitivity of the retina to visible light.[6]

1. Lerman S, *et al.* Potential ocular complications from PUVA therapy and their prevention. *J Invest Dermatol* 1980; 74: 197–9.
2. Woo TY, *et al.* Lenticular psoralen photoproducts and cataracts of a PUVA-treated psoriatic patient. *Arch Dermatol* 1985; 121: 1307–8.
3. See J-A, Weller P. Ocular complications of PUVA therapy. *Australas J Dermatol* 1993; 34: 1–4.
4. Stern RS, *et al.* Ocular findings in patients treated with PUVA. *J Invest Dermatol* 1985; 85: 269–73.
5. Penton DA, Wilkinson JD. Dose-related visual-field defects in patients receiving PUVA therapy. *Lancet* 1983; i: 1106.
6. Soutêtre R, *et al.* 5-Methoxypsoralen increases the sensitivity of the retina to light in humans. *Eur J Clin Pharmacol* 1989; 36: 59–61.

Effects on the hair. Hypertrichosis was noticed in 15 of 23 female patients receiving PUVA therapy compared with 2 of 14 patients treated with UVA alone.[1]

1. Rampen FHJ. Hypertrichosis in PUVA-treated patients. *Br J Dermatol* 1983; 109: 657–60.

Effects on the immune system. PUVA therapy appears to have immunosuppressive effects and inhibits lymphocytes, polymorphonuclear leucocytes, and Langerhans' cells.[1-3] It is capable of inducing antinuclear antibody formation and a syndrome similar to systemic lupus syndrome has developed during treatment.[4,5] An immunological basis has also been suspected for the development of nephrotic syndrome in one patient who received PUVA therapy.[6]

See also Hypersensitivity, below.

1. Farber EM, *et al.* Long-term risks of psoralen and UV-A therapy for psoriasis. *Arch Dermatol* 1983; 119: 426–31.
2. Morison WL, *et al.* Abnormal lymphocyte function following long-term PUVA therapy for psoriasis. *Br J Dermatol* 1983; 108: 445–50.
3. Chang A, *et al.* PUVA and UVB inhibit the intra-epidermal accumulation of polymorphonuclear leukocytes. *Br J Dermatol* 1988; 119: 281–7.
4. Bruze M, *et al.* Fatal connective tissue disease with antinuclear antibodies following PUVA therapy. *Acta Derm Venereol (Stockh)* 1984; 64: 157–60.
5. Bruze M, Ljunggren B. Antinuclear antibodies appearing during PUVA therapy. *Acta Derm Venereol (Stockh)* 1985; 65: 31–6.
6. Lam Thuon Mine LTK, *et al.* Nephrotic syndrome after treatment with psoralens and ultraviolet A. *BMJ* 1983; 287: 94–5.

Effects on the skin. *MALIGNANT NEOPLASMS.* Squamous cell carcinoma, basal cell carcinoma, keratoacanthoma, actinic keratosis, Bowen's disease, and malignant melanoma have all been reported during or after cessation of PUVA.[1-3] There have been several large long-term follow-up studies to assess the risk of **non-melanoma** skin cancer in patients receiving PUVA therapy. Early studies from Europe found no clear evidence that PUVA was independently carcinogenic but did find that previous treatment with arsenic, methotrexate, or ionising radiation increased the incidence of skin tumours.[4] Studies from the USA have found an increase in the incidence of basal cell carcinoma and squamous cell carcinoma independent of other treatment,[5] which was dose-related in some studies.[6] Male genitalia appeared to be particularly susceptible.[7] It has been suggested that the differences between the findings might be due to the fact that in Europe higher and fewer doses are used and the median total dose employed may be only 29% of that used in the USA.[8] However, further studies from northern Europe also found a dose-related increase in the risk of developing squamous cell carcinomas.[9-11] One small series suggested that about 50% of the recipients of high-dose PUVA went on to develop squamous cell carcinomas or premalignant lesions.[12] While some European workers have findings that confirm the increased susceptibility of the male genitalia[13] others have failed to find any such evidence.[14,15] Ongoing surveillance of patients is encouraged as US data[16,17] show the risk of skin cancers and genital tumours to persist long-term after stopping PUVA therapy. A few patients have gone on to develop metastatic disease.[18,19]

There are anecdotal reports of **malignant melanomas** occurring in patients who had received PUVA. A prospective study[20] in 1380 patients with psoriasis who were first treated with PUVA in 1975 or 1976 found that the risk of melanoma increases about 15 years after the first treatment with PUVA and that the risk was increased especially in patients who had received 250 treatments or more. The authors suggested that long-term PUVA should therefore be used with caution, especially in younger patients. Further follow-up of this group[21] found the incidence of melanoma to increase over time. However, a similar follow-up study[11] of 4799 patients treated with PUVA found no increase in the risk for malignant melanoma. Comparing their findings with the earlier study, the authors suggested that the results might differ because one-fifth of their cohort had received bath PUVA in which lower UVA doses are used. The comment has also been made[22] that patients receiving long-term therapy should be followed up carefully and that such therapy should not be used in patients at risk for melanoma.

A study[23] of follow-up data on patients who had received trioxysalen bath PUVA did not find an increase in risk of developing either squamous cell carcinoma or malignant melanoma, but the authors suggested that further study is needed to determine the carcinogenicity of trioxysalen PUVA.

1. Reshad H, *et al.* Cutaneous carcinoma in psoriatic patients treated with PUVA. *Br J Dermatol* 1984; 110: 299–305.
2. Kemmett D, *et al.* Nodular malignant melanoma and multiple squamous cell carcinomas in a patient treated by photochemotherapy for psoriasis. *BMJ* 1984; 289: 1498.
3. Suurmond D, *et al.* Skin cancer and PUVA maintenance therapy for psoriasis. *Br J Dermatol* 1985; 113: 685–6.
4. Henseler T, *et al.* Skin tumors in the European PUVA study. *J Am Acad Dermatol* 1987; 16: 108–16.
5. Forman AB, *et al.* Long-term follow-up of skin cancer in the PUVA-48 cooperative study. *Arch Dermatol* 1989; 125: 515–19.
6. Stern RS, *et al.* Non-melanoma skin cancer occurring in patients treated with PUVA five to ten years after first treatment. *J Invest Dermatol* 1988; 91: 120–4.
7. Stern RS, *et al.* Genital tumors among men with psoriasis exposed to psoralens and ultraviolet A radiation (PUVA) and ultraviolet B radiation. *N Engl J Med* 1990; 322: 1093–7.
8. Moseley H, Ferguson J. Photochemotherapy: a reappraisal of its use in dermatology. *Drugs* 1989; 38: 822–37.
9. Bruynzeel I, *et al.* High single-dose' European PUVA regimen also causes an excess of non-melanoma skin cancer. *Br J Dermatol* 1991; 124: 49–55.
10. Lindelöf B, *et al.* PUVA and cancer: a large-scale epidemiological study. *Lancet* 1991; 338: 91–3.
11. Lindelöf B, *et al.* PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 1999; 141: 108–12.
12. Lever LR, Farr PM. Skin cancers or premalignant lesions occur in half of high-dose PUVA patients. *Br J Dermatol* 1994; 131: 215–19.
13. Perkins W, *et al.* Cutaneous malignancy in males treated with photochemotherapy. *Lancet* 1990; 336: 1248.
14. Wolff K, Hönigsmann H. Genital carcinomas in psoriasis patients treated with photochemotherapy. *Lancet* 1991; 337: 439.
15. Aubin F, *et al.* Genital squamous cell carcinoma in men treated by photochemotherapy: a cancer registry-based study from 1978 to 1998. *Br J Dermatol* 2001; 144: 1204–6.
16. Stern RS, *et al.* The persistent risk of genital tumors among men treated with psoralen plus ultraviolet A (PUVA) for psoriasis. *J Am Acad Dermatol* 2002; 47: 33–9.
17. Nijsten TEC, Stern RS. The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 2003; 121: 252–8.
18. Lewis FM, *et al.* Metastatic squamous-cell carcinoma in patient receiving PUVA. *Lancet* 1994; 344: 1157.
19. Stern RS. Metastatic squamous cell cancer after psoralen photochemotherapy. *Lancet* 1994; 344: 1644–5.
20. Stern RS, *et al.* Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; 336: 1041–5.
21. Stern RS. The PUVA Follow Up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001; 44: 755–61.
22. Wolff K. Should PUVA be abandoned? *N Engl J Med* 1997; 336: 1090–1.
23. Hannuksela-Svahn A, *et al.* Trioxsalen bath PUVA did not increase the risk of squamous cell skin carcinoma and cutaneous malignant melanoma in a joint analysis of 944 Swedish and Finnish patients with psoriasis. *Br J Dermatol* 1999; 141: 497–501.

NON-MALIGNANT SKIN DISORDERS. Toxic pustuloderma, marked by erythema and superficial pustular lesions, has been reported in a patient given PUVA therapy for mycosis fungoides.[1] Bullous pemphigoid occurring, or recurring, has been seen in patients treated with PUVA, usually for psoriasis.[2] A case of lichen planus pemphigoides has also been described in a woman treated with topical PUVA.[3] Another effect sometimes associated with PUVA is severe skin pain;[4,5] the pain may respond to treatment with topical capsaicin.[5] Long-term PUVA treatment accelerates ageing of the skin.[6]

1. Yip J, *et al.* Toxic pustuloderma due to PUVA treatment. *Br J Dermatol* 1991; 125: 401–2.
2. Barnadas MA, *et al.* Bullous pemphigoid in a patient with psoriasis during the course of PUVA therapy: study by ELISA test. *Int J Dermatol* 2006; 45: 1089–92.
3. Kuramoto N, *et al.* PUVA-induced lichen planus pemphigoides. *Br J Dermatol* 2000; 142: 509–12.
4. Burrows NP, *et al.* PUVA-induced skin pain. *Br J Dermatol* 1993; 129: 504.
5. Burrows NP, Norris PG. Treatment of PUVA-induced skin pain with capsaicin. *Br J Dermatol* 1994; 131: 584–5.
6. Sator P-G, *et al.* Objective assessment of photoageing effects using high-frequency ultrasound in PUVA-treated psoriasis patients. *Br J Dermatol* 2002; 147: 291–8.

Hypersensitivity. Hypersensitivity reactions to methoxsalen and PUVA therapy occur rarely but there have been reports of drug-induced fever,[1] bronchoconstriction,[2] and contact dermatitis.[3] Cases of anaphylaxis have also been attributed to methoxsalen[4] and 5-methoxypsoralen.[5]

1. Tóth Kása I, Dobozy A. Drug fever caused by PUVA treatment. *Acta Derm Venereol (Stockh)* 1985; 65: 557–8.
2. Ramsay B, Marks JM. Bronchoconstriction due to 8-methoxypsoralen. *Br J Dermatol* 1988; 119: 83–6.
3. Takashima A, *et al.* Allergic contact and photocontact dermatitis due to psoralens in patients with psoriasis treated with topical PUVA. *Br J Dermatol* 1991; 124: 37–42.
4. Park JY, *et al.* Anaphylaxis to 8-methoxypsoralen during photochemotherapy. *Photodermatol Photoimmunol Photomed* 2003; 19: 37–8.
5. Legat FJ, *et al.* Anaphylaxis to 5-methoxypsoralen during photochemotherapy. *Br J Dermatol* 2001; 145: 821–2.

Precautions

Methoxsalen should not generally be given to patients with diseases associated with light sensitivity such as porphyria, although it may be used with care in some photosensitivity disorders to decrease sensitivity to sunlight. Other contra-indications include aphakia, melanoma or a history of melanoma, and invasive squamous cell carcinoma. It is generally recommended that PUVA therapy should not be used in children. Methoxsalen should be used with caution in patients with hepatic impairment.

Patients should not sunbathe for 24 hours before and 48 hours after PUVA treatment. They should avoid exposure to sunlight, even through glass or cloud cover for at least 8 hours after methoxsalen ingestion and should wear wrap-around UVA absorbing glasses for 24 hours after ingestion. Photosensitivity is more prolonged after topical application and treated skin should be protected from exposure to sunlight for at least 12 to 48 hours, and possibly for up to a week. Unless specific treatment is required male genitalia should be shielded during PUVA therapy. It has been recommended that patients undergo an ophthalmic examination before starting therapy and at regular intervals thereafter, especially those at increased risk of cataracts. Patients should also receive regular examinations for signs of premalignant or malignant skin lesions. Anti-nuclear antibody titre may be tested before starting therapy, particularly if there is a suggestion of connective tissue disease; frequent evaluation during treatment is probably not necessary for patients with uncomplicated psoriasis, an initial negative test, and no symptoms of connective tissue disease.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies methoxsalen as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Methoxsalen should be used with caution with other drugs also known to cause photosensitivity. It inhibits the action of cytochrome P450 isoenzyme CYP2A6, and may increase plasma concentrations of drugs metabolised via this enzyme.

Antiepileptics. Failure of PUVA treatment due to abnormally low serum concentrations of methoxsalen in a patient with epilepsy was probably a result of induction of hepatic enzymes by *phenytoin*.[1]

1. Staberg B, Hueg B. Interaction between 8-methoxypsoralen and phenytoin. *Acta Derm Venereol (Stockh)* 1985; 65: 553–5.

Emollients. Some emollient preparations may have a photoprotective effect, and if applied immediately before UVA irradiation could interfere with the efficacy of PUVA therapy.[1,2]

1. Hudson-Peacock MJ, *et al.* Photoprotective action of emollients in ultraviolet therapy of psoriasis. *Br J Dermatol* 1994; 130: 361–5.
2. Otman SGH, *et al.* Modulation of ultraviolet (UV) transmission by emollients: relevance to narrowband UVB phototherapy and psoralen plus UVA photochemotherapy. *Br J Dermatol* 2006; 154: 963–8.

Food. Some foods, for example, celery, parsnip, and parsley, contain psoralens and eating large quantities may increase the risk of phototoxicity with methoxsalen. A patient[1] who ate a large quantity of celery soup the evening before and 2 hours before undergoing PUVA therapy for atopic eczema developed severe phototoxicity after treatment, which was attributed to the additive effects of methoxsalen and psoralens contained in the celery.

1. Boffa MJ, *et al.* Celery soup causing severe phototoxicity during PUVA therapy. *Br J Dermatol* 1996; 135: 334.

Melatonin. For the effect of methoxsalen on melatonin, see p. 2552.2.

Xanthines. For mention of the effect of systemic methoxsalen on the metabolism of theophylline, see Methoxsalen, under Interactions of Theophylline, p. 1236.2.

Pharmacokinetics

When taken orally methoxsalen is well but variably absorbed from the gastrointestinal tract and there is considerable interindividual variation in peak serum concentrations. Depending on the oral formulation used increased photosensitivity is present 1 hour after a dose, reaches a peak at about 1 to 4 hours, and disappears after about 8 hours. Methoxsalen is highly protein bound. It appears to be preferentially taken up by epidermal cells. It also diffuses into the lens of the eye. Methoxsalen is almost completely metabolised. About 95% of a dose is excreted in the urine within 24 hours. The photosensitising action of methoxsalen may persist for several days after topical application. The erythema induced by oral or topical PUVA is usually delayed and peaks after 2 to 3 days.

References.

1. de Wolff FA, Thomas TV. Clinical pharmacokinetics of methoxsalen and other psoralens. *Clin Pharmacokinet* 1986; 11: 62–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Oxsoralen Ultra; *Austral.*: Oxsoralen†; *Austria*: Oxsoralen; *Belg.*: Mopsoralen; *Braz.*: Oxsoralen; *Canad.*: Oxsoralen; Ultramop†; *Chile*: Oxsoralen; *China*: Meladinine (敏柏宁); *Cz.*: Oxsoralen; Uvadex; *Fr.*: Meladinine; Uvadex; *Ger.*: Meladinine; Uvadex; *Gr.*: Melaoline; Uvadex; *Hong Kong*: Oxsoralen; *Hung.*: Oxsoralen; *India*: Manaderm†; Meladerm; Melanocyl; Melcyl; Melonil; *Indon.*: Delsoralen; Oxsoralen; *Irl.*: Deltasoralen†; *Jpn*: Oxsoralen; *Malaysia*: Oxsoralen†; *Mex.*: Dermox; Meladinina; Oxsoralen; *Neth.*: Geroxalen; Uvadex; *NZ*: Oxsoralen†; *Pol.*: Geralen†; Oxsoralen; *Port.*: Uvadex; *Rus.*: Oxsoralen (Оксорален); *S.Afr.*: Oxsoralen†; *Singapore*: Meladinine†; Oxsoralen; *Spain*: Oxsoralen; *Switz.*: Meladinine†; Uvadex†; *Thai.*: Meladinine; *Turk.*: Geroxalen; Vitpso; *UK*: Puvasoralen; *USA*: Oxsoralen; Uvadex.

Multi-ingredient Preparations. *India*: Melanocyl; Melonil.

Pharmacopoeial Preparations
USP 36: Methoxsalen Capsules; Methoxsalen Topical Solution.

5-Methoxypsoralen

Bergapteeni; Bergapten; Bergaptenо; Bergaptenum; 5-Metoxipsoraleno; 5-MOP; 5-Метоксипсорален.
4-Methoxy-7*H*-furo[3,2-*g*]chromen-7-one.
$C_{12}H_8O_4$=216.2
CAS — 484-20-8.
ATC — D05BA03.
ATC Vet — QD05BA03.
UNII — 4FVK84C92X.

Profile

5-Methoxypsoralen is a photosensitiser with actions similar to those of methoxsalen (p. 1711.3). It may be given orally in the PUVA therapy (see under Methoxsalen, p. 1712.1) of psoriasis and vitiligo.

5-Methoxypsoralen is included in some cosmetic suntan preparations to enhance tanning but because of its potential phototoxicity this is considered unwise by authorities in Europe and the USA. Photosensitivity caused by 5-methoxypsoralen is sometimes known as Berloque dermatitis.

5-Methoxypsoralen is an ingredient of bergamot oil (p. 2455.1).

References.

1. McNeely W, Goa KL. 5-Methoxypsoralen: a review of its effects in psoriasis and vitiligo. *Drugs* 1998; 56: 667–90.

Hypersensitivity. For mention of anaphylaxis associated with the use of 5-methoxypsoralen, see Hypersensitivity, under Adverse Effects of Methoxsalen, p. 1713.3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Geralen; *UK*: Pentaderm.

Methyl Anthranilate

Metilo, antranilato de; Metylu antranilan; Метилантранилат.
Methyl 2-aminobenzoate.
$C_8H_9NO_2$=151.2
CAS — 134-20-3.
UNII — 981I0C1E5W.

NOTE. Do not confuse with menthyl anthranilate (see Meradimate, p. 1711.2).

Profile

Methyl anthranilate has been used in sunscreen preparations. It is a constituent of several essential oils.

Mexenone *(BAN, pINN)*

Benzofenon-10; Benzophenone-10; Mexenona; Mexénone; Mexenonum; Мексенон.
2-Hydroxy-4-methoxy-4′-methylbenzophenone.
$C_{15}H_{14}O_3$=242.3
CAS — 1641-17-4.
UNII — ET1UGF4A0B.

Pharmacopoeias. In *Br.*

BP 2014: (Mexenone). A pale yellow odourless or almost odourless crystalline powder. Practically insoluble in water; sparingly soluble in alcohol; freely soluble in acetone.

Profile

Mexenone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3)

Preparations

Pharmacopoeial Preparations
BP 2014: Mexenone Cream.

Monobenzone *(rINN)*

Benoquina; Éter monobencílico de la hidroquinona; Hydroquinone Monobenzyl Ether; Monobenzona; Monobenzonum; Монобензон.
4-Benzyloxyphenol.
$C_{13}H_{12}O_2$=200.2
CAS — 103-16-2.
ATC — D11AX13.
ATC Vet — QD11AX13.
UNII — 9L2KA76MG5.

Pharmacopoeias. In *US.*

USP 36: (Monobenzone). Store at a temperature not exceeding 30 degrees in airtight containers. Protect from light.

Uses and Administration

Monobenzone has actions similar to those of hydroquinone (p. 1705.1) but in some patients it also produces extensive and selective destruction of melanocytes. It is used locally for final, permanent depigmentation of normal skin in extensive vitiligo (see Pigmentation Disorders, p. 1687.2). Monobenzone is not recommended for freckling, chloasma, or hyperpigmentation following skin inflammation or due to photosensitisation after the use of certain perfumes. It has no effect on melanomas or pigmented naevi.

For vitiligo a cream containing monobenzone 20% is applied to the affected areas two or three times daily until a satisfactory response is obtained, and thereafter as necessary, usually about twice weekly. Depigmentation only becomes apparent when the preformed melanin pigments have been lost with the normal sloughing of the stratum corneum and this may take several months. If, however, no improvement is noted after 4 months, treatment should be stopped. Excessive exposure to sunlight should be avoided during treatment. After depigmentation the skin will be sensitive for the rest of the patient's life and a sunscreen must be used during sun exposure.

Adverse Effects and Precautions

Monobenzone may cause skin irritation and sensitisation. In some patients this is transient and the drug need not be withdrawn. In others, an eczematous sensitisation may occur. Excessive depigmentation may occur even beyond the areas under treatment and may produce unsightly patches.

Monobenzone frequently produces permanent depigmentation and should not be used as a substitute for hydroquinone.

Interactions

Agalsidase. For the recommendation that monobenzone not be used with agalsidase alfa or beta, see p. 2438.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Benoquin; *India*: Benoquin; *USA*: Benoquin†.

Pharmacopoeial Preparations
USP 36: Monobenzone Cream.

Monochloroacetic Acid

Chloroacetic Acid; Kwas chlorooctowy; Monocloroacético, ácido; Монохлоруксусная Кислота.
$C_2H_3O_2Cl$=94.49
CAS — 79-11-8.
UNII — 5GD84Y125G.

Profile

Preparations containing 50% of monochloroacetic acid are used as a caustic for the removal of plantar warts (p. 1689.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Warzenmittel†; *Switz.*: Acetocaustine; *USA*: Monocete.

Multi-ingredient Preparations. *Turk.*: IL-33.

Motretinide *(USAN, rINN)*

Motretinid; Motretinida; Motrétinide; Motretinidi; Motretinidum; Ro-11-1430; Мотретинид.
(*all-trans*)-*N*-Ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenamide.
$C_{23}H_{31}NO_2$=353.5
CAS — 56281-36-8.
ATC — D10AD05.
ATC Vet — QD10AD05.
UNII — W786807KL1.

Profile

Motretinide is a retinoid structurally related to acitretin (p. 1690.3). Motretinide is used topically in the treatment of acne (p. 1682.2). It is applied in preparations containing 0.1%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Tasmaderm.

Nalfurafine Hydrochloride *(USAN, rINNM)*

AC-820; Hidrocloruro de nalfurafina; Nalfurafine, Chlorhydrate de; Nalfurafini Hydrochloridum; TRK-820; Нальфурафина Гидрохлорид.
(*E*)-*N*-[17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6β-yl]-3-(furan-3-yl)-*N*-methylprop-2-enamide hydrochloride.
$C_{28}H_{32}N_2O_5$,HCl=513.0
CAS — 152657-84-6 (nalfurafine); 152658-17-8 (nalfurafine hydrochloride).
ATC — V03AX01; V03AX02.
ATC Vet — QV03AX02.
UNII — 25CC4N0P8J.

Profile

Nalfurafine hydrochloride is a selective κ-opioid receptor agonist that is used in the management of treatment-resistant pruritus (p. 1687.3) in haemodialysis patients. It is given orally in a dose of 2.5 micrograms once daily in the evening, which may be increased to 5 micrograms once daily if required.

References.

1. Wikström B, *et al.* κ-Opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005; 16: 3742–7.

2. Nakao K, Mochizuki H. Nalfurafine hydrochloride: a new drug for the treatment of uremic pruritus in hemodialysis patients. *Drugs Today* 2009; 45: 323–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Remitch.

Naphthalan Liquid

Naftalan; Naphthalanic Oil; Naphthalanum Liquidum; Нафталановое Масло.

CAS — 37229-16-6.

Profile

Naphthalan liquid is an oil-like complex mixture of naphthene hydrocarbons and tars obtained from the oil fields of Azerbaijan and Croatia. It has analgesic, anti-inflammatory, and emollient properties and is used in the treatment of conditions such as psoriasis and in various musculoskeletal disorders. It is usually applied locally in the form of the oil or as an ointment or alternatively patients may bath in the oil.

References.

1. Vrzogić P, *et al.* Naphthalan – a natural medicinal product. *Acta Dermatovenerol Croat* 2003; 11: 178–84.

Octil Triazone

Ethylhexyl Triazone; Octiltriazona; Octyl Triazone; Октилтриазон.

2,4,6-Trianilino-*p*-(carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine.

$C_{48}H_{66}N_6O_6$=823.1

CAS — 88122-99-0.

NOTE. Uvinul T 150 is a trade name that has been used for octil triazone.

Profile

Octil triazone is used as a sunscreen (p. 1681.3). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cetaphil UV Defense; Fotoprotector Extrem; Fotoprotector; Leico Ultrablock Extreme; Leico Ultrablock†; *Austral.*: Hamilton Quadblock; Sunsense Daily Face; Sunsense Moisturising Face; Sunsense Toddler Milk; Sunsense; *Braz.*: Anthelios Helioblock Spray; Anthelios Helioblock W30; Helioblock†; Sunmax 60; Sunmax Acqua; *Chile*: Ansolar; Ansolar; Emolan Gel Protector Solar; Eucerin Solar†; Eucerin; Eucerin; Fotoprotector Isdin Extrem Pediatrics; Fotoprotector Isdin Extrem†; Hyaluron; Nutraisdin; Photoderm AR†; Photoderm Max†; Photoderm Spot†; Uriage Crema Color; Uriage Crema Extra; Uriage Protector Solar†; *Fr.*: Anthelios; Anthelios; Anthelios; SVR 100†; *Ger.*: Daylong actinica†; *Hong Kong*: Sunsense Clear Mist†; Sunsense Daily Face; Sunsense Toddler Milk; *Malaysia*: Cetaphil UVA/UVB Defense; Sunsense Clear Mist†; Sunsense Daily Face; Sunsense Toddler Milk; *Mex.*: Dermaglos Solar†; *NZ*: Aquasun; Hamilton Quadblock; *Singapore*: Cetaphil UVA/UVB; Sunsense Clear†; Sunsense Daily Face; Sunsense Moisturising Face; Sunsense Toddler Milk; *Switz.*: Daylong actinica; *Thai.*: Eucerin Sun Sensitive Skin†; *UK*: Anthelios XL; *Venez.*: Photoderm Max; Photoderm.

Octinoxate *(USAN, rINN)*

Ocinoxate; Octinoxato; Octinoxatum; Octyl methoxycinnamate; Оциноксат.

2-Ethylhexyl-*p*-methoxycinnamate; 3-(4-Methoxylphenyl)-2-propenoic acid 2-ethylhexyl ester.

$C_{18}H_{26}O_3$=290.4

CAS — 5466-77-3

ATC — D02BA02

ATC Vet — QD02BA02

UNII — 4Y5P7MUD51.

NOTE. Escalol 557, Eusolex 2292, Neo-Heliopan AV, Parsol MCX, Tinosorb OMC, Uvinul MC 80, and Uvinul MC 80 N are trade names that have been used for octinoxate.

Pharmacopoeias. In *US*.

USP 36: (Octinoxate). Pale yellow oil. Insoluble in water. Store in airtight containers at a temperature of 8 degrees to 15 degrees.

Profile

Octinoxate, a substituted cinnamate, is used by topical application as a sunscreen (p. 1681.3). Cinnamate sunscreens effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Cinnamate sunscreens may therefore be used to prevent sunburn but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection against such photosensitivity. Cinnamates may occasionally produce photosensitivity reactions.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Blistex Lip Conditioning Balm; Clear Zinke; *Braz.*: Solaquin; *Canad.*: Almay Hydracolor Lipstick†; Almay TLC Truly Lasting†; Anti-Aging Foundation: Aqua Fusion Teinte†; Aquaradiance†; Aquasource; Avon Beyond: Avon Sun Self-Tanning†; Ceramide Time Complex; Clinique Skin Supplies; Diorskin Sculpt; Feel Naturale†; Finish†; Hawaiian Tropic Dark Tanning†; Hawaiian Tropic Oil; Healthy Makeup†; Lip Balm; Luxiva Sheer Defense; Mac Hyper Real†; Mac Mineralize; Mac Select Tint†; Marcelle Sheer Tint; Moisture Extreme†; Photogenic Lumessence; Prescriptives Incredible†; Revlon Lipgloss†; Revlon Super Lustrous†; Sense Matte†; Sheer Protection†; Shiseido Benefiance Daytime; Shiseido Benefiance Daytime; Silkies Enriche; Skin Caviar; Ultra Color Rich Cool Bliss†; Ultra Facial Tinted Moisturizer; Visible Lift†; Vitalumiere; *Chile*: ROC Minesol Bronze; *NZ*: Hamilton Sunscreen†; *Singapore*: Sunsense Anti-Ageing; *USA*: Coppertone Tan Magnifier; Neutrogena Glow; Neutrogena Moisture.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Octisalate *(USAN, rINN)*

Octisalato; Octisalatum; Octyl Salicylate; Октисалат.

2-Ethylhexyl salicylate; 2-Hydroxybenzoic acid 2-ethylhexyl ester.

$C_{15}H_{22}O_3$=250.3

CAS — 118-60-5.

UNII — 4X49Y0596W.

NOTE. Escalol 587, Eusolex OS, and Neo-Heliopan OS are trade names that have been used for octisalate.

Pharmacopoeias. In *US*.

USP 36: (Octisalate). Store in airtight containers.

Profile

Octisalate is a substituted salicylate used topically as a sunscreen (p. 1681.3). Salicylates effectively absorb light throughout the UVB range but absorb little or no UVA light (for definitions, see p. 1685.3). Salicylate sunscreens may therefore be used to prevent sunburn, but are unlikely to prevent drug-related or other photosensitivity reactions associated with UVA light; combination with a benzophenone may give some added protection.

Salicylates may occasionally produce photosensitivity reactions or contact dermatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Leico; *Canad.*: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; *Chile*: ROC Minesol Bronze.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Octocrilene *(rINN)*

2-Ethylhexyl α-cyano-β-phenylcinnamate; Octocrilène; Octocrileno; Octocrilenum; Octocrylene (USAN); Octocrylène; Октокрилен.

2-Ethylhexyl 2-cyano-3,3-diphenylacrylate.

$C_{24}H_{27}NO_2$=361.5

CAS — 6197-30-4.

UNII — 5A68WGF6WM.

NOTE. Escalol 597, Eusolex OCR, Neo-Heliopan 303, Parsol 340, and Uvinul N 539 T are trade names that have been used for octocrilene.

Pharmacopoeias. In *US*.

USP 36: (Octocrylene). Store in airtight containers.

Profile

Octocrilene, a substituted cinnamate, is a sunscreen (p. 1681.3) with actions similar to those of octinoxate (above). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Coppertone Oil-Free Sunscreen.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Oxybenzone *(USAN, rINN)*

Benzofenon-3; Benzophenone-3; Oxibenzona; Oxybenzonum; Оксибензон.

2-Hydroxy-4-methoxybenzophenone.

$C_{14}H_{12}O_3$=228.2

CAS — 131-57-7.

UNII — 95OOS7VE0Y.

NOTE. Escalol 567, Eusolex 4360, Neo-Heliopan BB, Tinosorb B3, and Uvinul M 40 are trade names that have been used for oxybenzone.

Pharmacopoeias. In *US*.

USP 36: (Oxybenzone). A pale yellow powder. Practically insoluble in water; freely soluble in alcohol and in toluene. Store in airtight containers. Protect from light.

Profile

Oxybenzone is a substituted benzophenone used topically as a sunscreen (p. 1681.3). Benzophenones effectively absorb light throughout the UVB range (wavelengths 290 to 320 nm) and also absorb some UVA light with wavelengths of 320 to about 360 nm and some UVC light with wavelengths of about 250 to 290 nm (for definitions, see p. 1685.3). Benzophenones may therefore be used to prevent sunburn and may also provide some protection against drug-related or other photosensitivity reactions associated with UVA light; in practice they are usually combined with a sunscreen from another group.

Photocontact allergic dermatitis can be caused by topical application of benzophenone sunscreens. Oxybenzone is widely used and often found to be a photo-allergen in patients with these reactions. Contact allergy reactions occur less frequently.

Hypersensitivity. Chemical sunscreens are known to cause photosensitivity and contact allergy reactions. Oxybenzone is widely used and reported to be the sunscreen photo-allergen most commonly detected in photopatch testing.[1,2] In a group of 5800 patients with suspected allergic contact dermatitis who were tested for contact allergens,[3] a positive reaction to oxybenzone was recorded in 0.6%. There have also been rare reports of severe allergic reactions to oxybenzone including anaphylaxis; sensitivity was confirmed by patch testing.[4,5] A history of atopy may predispose patients to such reactions.

1. Berne B, Ros A-M. 7 years experience of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 1998; 38: 61–4.
2. Bryden AM, *et al.* Photopatch testing of 1155 patients: results of the U.K. multicentre photopatch study group. *Br J Dermatol* 2006; 155: 737–47.
3. Marks JG, *et al.* North American Contact Dermatitis Group patch-test results, 1998 to 2000. *Am J Contact Dermat* 2003; 14: 59–62.
4. Emonet S, *et al.* Anaphylaxis to oxybenzone, a frequent constituent of sunscreens. *J Allergy Clin Immunol* 2001; 107: 556–7.
5. Yesudian PD, King CM. Severe contact urticaria and anaphylaxis from benzophenone-3 (2-hydroxy 4-methoxy benzophenone). *Contact Dermatitis* 2002; 46: 55–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biorevit Labial; Leico; *Braz.*: Solaquin; *Canad.*: Clinique Skin Supplies; Coppertone Oil-Free Sunscreen; Silkies Enriche.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

USP 36: Dioxybenzone and Oxybenzone Cream.

Padimate *(BAN, rINN)*

Amyl Dimethylaminobenzoate; Isoamyl Dimethylaminobenzoate; Padimate A (USAN); Padimate A; Padimato; Padimatum; Падимат.

A mixture of pentyl, isopentyl, and 2-methylbutyl 4-dimethylaminobenzoates.

$C_{14}H_{21}NO_2$=235.3

CAS — 14779-78-3 (pentyl 4-dimethylaminobenzoate); 21245-01-2 (isopentyl 4-dimethylaminobenzoate).

UNII — 77FU10423X.

Profile

Padimate, a substituted aminobenzoate, is a sunscreen (p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Uvless; *Canad.*: Solaquin Forte; *USA*: Vaseline Intensive Care Blockout.

Padimate O (BANM, USAN)

Ethylhexyl Dimethyl PABA; Octyl Dimethyl PABA; Padimato O; Падимат О.

2-Ethylhexyl 4-(dimethylamino)benzoate.

$C_{17}H_{27}NO_2$=277.4

CAS — 21245-02-3.

UNII — Z1006CMUZ.

NOTE. Escalol 507 and Eusolex 6007 are trade names that have been used for padimate O.

Pharmacopoeias. In *US.*

USP 36: (Padimate O). A light yellow, mobile liquid with a faint aromatic odour. Practically insoluble in water, in glycerol, and in propylene glycol; soluble in alcohol, in isopropyl alcohol, and in liquid paraffin. Store in airtight containers. Protect from light.

Profile

Padimate O, a substituted aminobenzoate, is a sunscreen (p. 1681.3) with actions similar to those of aminobenzoic acid (p. 1694.2). It is effective against UVB light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Chapstick; Iluminoderm; Vunsu; Womosol; *Austral.*: Chapstick†; *Braz.*: Solaquin; *Canad.*: Saving Face†; *Chile*: Chapstick Mint; Emolan H.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
USP 36: Padimate O Lotion.

Pimecrolimus (BAN, USAN, rINN)

ASM-981; Pimécrolimus; Pimecrolimús; Pimecrolimusum; Pimekrolimus; Pimekrolimuusi; SDZ-ASM-981; Пимекролимус.

(3*S*,4*R*,5*S*,8*R*,9*E*,12*S*,14*S*,15*R*,16*S*,18*R*,19*R*,26a*S*)-3-[(*E*)-2-[(1*R*,3*R*,4*S*)-4-Chloro-3-methoxycyclohexyl]-1-methylvinyl]-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclotricosine-1,7,20,21(4*H*,23*H*)-tetrone.

$C_{43}H_{68}ClNO_{11}$=810.5

CAS — 137071-32-0.

ATC — D11AH02.

ATC Vet — QD11AH02.

UNII — 7KYV510875.

Uses and Administration

Pimecrolimus is a macrolactam ascomycin derivative related to tacrolimus (p. 1968.3) that acts as a calcineurin inhibitor and has similar anti-inflammatory and immunosuppressant actions. It is used topically for short-term and intermittent long-term treatment of mild to moderate atopic eczema (p. 1684.1) in non-immunocompromised patients over the age of 2 years when conventional therapies are ineffective or unsuitable. Pimecrolimus is applied twice daily as a 1% cream until signs and symptoms clear. Treatment should be stopped if there is no improvement after 6 weeks or if eczema is exacerbated.

Oral forms of pimecrolimus are also being investigated for the treatment of psoriasis and atopic eczema.

Administration in infants. A review[1] of data from 10 studies that included 1133 infants between 3 and 23 months of age who were treated with topical pimecrolimus 1% cream for up to 2 years found that the level of systemic exposure to pimecrolimus was very low and comparable to that seen in older children and adults. Treatment was reported to be effective and there was no evidence of immunosuppression or an increase in the rate of infections. Licensed product information, however, does not recommend its use in patients under 2 years of age as the effect of pimecrolimus cream on the developing immune system in infants is unknown (for concerns about possible carcinogenicity see below).

1. Paul C, *et al.* Safety and tolerability of 1% pimecrolimus cream among infants: experience with 1133 patients treated for up to 2 years. Abstract: *Pediatrics* 2006; 117: 202–3. Full version: http://pediatrics.aappublications.org/cgi/reprint/117/1/e118 (accessed 27/09/07)

Eczema. The use of topical pimecrolimus in eczema has been the subject of reviews and meta-analyses,[1-3] generally concluding that it is less effective than moderate or potent corticosteroids or tacrolimus;[2,3] there is also a lack of studies comparing efficacy with mild corticosteroids.[2,3] For the use of topical pimecrolimus specifically in infants, see above.

Oral use of pimecrolimus has also been the subject of one trial[4] although it was noted that further study was required.

1. Wellington K, Jarvis B. Topical pimecrolimus: a review of its clinical potential in the management of atopic dermatitis. *Drugs* 2002; 62: 817–40.
2. Ashcroft DM, *et al.* Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomised controlled trials. *BMJ* 2005; 330: 516–22.
3. Ashcroft DM, *et al.* Topical pimecrolimus for eczema. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 12/04/10).
4. Wolff K, *et al.* Efficacy and tolerability of three different doses of oral pimecrolimus in the treatment of moderate to severe atopic dermatitis: a randomized controlled trial. *Br J Dermatol* 2005; 152: 1296–1303.

Lichen. There are a few case reports[1,2] of benefit from pimecrolimus 1% cream in the management of oral *lichen planus* (p. 1685.2). In most cases it was applied twice daily, and in some cases adhesive gel or paste was also used. Improvement in oral lesions occurred within 2 to 4 weeks in 3 cases.[1] In 3 small randomised, placebo-controlled studies[1,3-5] of patients with erosive disease, pimecrolimus 1% cream was applied twice daily for about 4 weeks, with varying results. Although pain scores were reduced with pimecrolimus, the reduction in erythema was not maintained in one study.[3] There was also a trend towards an improvement in ulceration but changes in scores were not statistically significant. The other 2 studies noted more significant reductions in pain and extent of erosion, with one[5] suggesting a possible sustained remission seen after treatment was stopped, whilst the other[4] contradicts this. In some patients who did not respond in the first month of treatment therapy for another month did prove beneficial.[5] Topical pimecrolimus has also been tried in the management of genital lichen planus. In a series[6] of 11 women, 9 noted benefit after 4 to 6 weeks of treatment; with follow-up of up to 10 months, 6 of them had had a complete response and 3 a partial response.

The resolution of signs and symptoms of *lichen sclerosus* (p. 1685.2) has been reported in 7 female patients (aged 4 to 48 years) with the use of topical pimecrolimus 1% cream twice daily for 3 to 4 months.[7,8] A poor response was reported in a 62-year-old woman who used the cream less frequently because of burning and stinging.[7]

1. Esquivel-Pedraza L, *et al.* Treatment of oral lichen planus with topical pimecrolimus 1% cream. *Br J Dermatol* 2004; 150: 771–3.
2. Dissemond J, *et al.* Pimecrolimus in an adhesive ointment as a new treatment option for oral lichen planus. *Br J Dermatol* 2004; 150: 782–4.
3. Swift JC, *et al.* The effectiveness of 1% pimecrolimus cream in the treatment of oral erosive lichen planus. *J Periodontol* 2005; 76: 627–35.
4. Passeron T, *et al.* Treatment of oral erosive lichen planus with 1% pimecrolimus cream: a double-blind, randomized, prospective trial with measurement of pimecrolimus levels in the blood. *Arch Dermatol* 2007; 143: 472–6.
5. Volz T, *et al.* Pimecrolimus cream 1% in erosive oral lichen planus—a prospective randomized double-blind vehicle-controlled study. *Br J Dermatol* 2008; 159: 936–41.
6. Lonsdale-Eccles AA, Velangi S. Topical pimecrolimus in the treatment of genital lichen planus: a prospective case series. *Br J Dermatol* 2005; 153: 390–4.
7. Goldstein AT, *et al.* Pimecrolimus for the treatment of vulvar lichen sclerosus: a report of 4 cases. *J Reprod Med* 2004; 49: 778–80.
8. Borns S, *et al.* Pimecrolimus 1% cream for anogenital lichen sclerosus in childhood. *BMC Dermatol* 2004; 4: 14. Available at: http://www.biomedcentral.com/1471-5945/4/14 (accessed 27/09/07)

Psoriasis. Topical pimecrolimus may have some benefit[1] in the treatment of psoriasis (p. 1688.1). Although studies have generally found it to be less effective than topical corticosteroids or topical calcipotriol,[2-4] one study[2] in patients with chronic plaque psoriasis did report that pimecrolimus 1% ointment applied under occlusion had a similar efficacy to clobetasol propionate 0.05% ointment.

Oral pimecrolimus is also under investigation and has reduced disease severity in dose-finding studies in patients with chronic plaque psoriasis.[5,6]

1. Gribetz C, *et al.* Pimecrolimus cream 1% in the treatment of intertriginous psoriasis: a double-blind, randomized study. *J Am Acad Dermatol* 2004; 51: 731–8.
2. Mrowietz U, *et al.* The novel ascomycin derivative SDZ ASM 981 is effective for psoriasis when used topically under occlusion. *Br J Dermatol* 1998; 139: 992–6.
3. Mrowietz U, *et al.* An experimental ointment formulation of pimecrolimus is effective in psoriasis without occlusion. *Acta Derm Venereol* 2003; 83: 351–3.
4. Kreuter A, *et al.* 1% Pimecrolimus, 0.005% calcipotriol, and 0.1% betamethasone in the treatment of intertriginous psoriasis: a double-blind, randomized controlled study. *Arch Dermatol* 2006; 142: 1138–43.
5. Rappersberger K, *et al.* Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. *J Invest Dermatol* 2002; 119: 876–87.
6. Gottlieb AB, *et al.* Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized, dose-finding trial. *Br J Dermatol* 2005; 152: 1219–27.

Seborrhoeic dermatitis. Small studies[1,2] suggest that topical pimecrolimus has a similar efficacy to topical corticosteroids in the treatment of seborrhoeic dermatitis (p. 1689.1). It has also been effective in a few cases that had not responded to topical corticosteroids.[3]

1. Rigopoulos D, *et al.* Pimecrolimus cream 1% vs. betamethasone 17-valerate 0.1% cream in the treatment of seborrhoeic dermatitis: a randomized open-label clinical trial. *Br J Dermatol* 2004; 151: 1071–5.
2. Firooz A, *et al.* Pimecrolimus cream, 1%, vs hydrocortisone acetate cream, 1%, in the treatment of facial seborrheic dermatitis: a randomized, investigator-blind, clinical trial. *Arch Dermatol* 2006; 142: 1066–7.
3. Cunha PR. Pimecrolimus cream 1% is effective in seborrhoeic dermatitis refractory to treatment with topical corticosteroids. *Acta Derm Venereol* 2006; 86: 69–70.

Adverse Effects and Precautions

As for topical tacrolimus (p. 1971.1).

The most frequent adverse effects of topical pimecrolimus are a burning sensation, irritation, pruritus, erythema, and folliculitis at the application site. Uncommon effects include skin papilloma and various bacterial and viral skin infections. Rarely anaphylactic reactions, sometimes severe, have been reported.

Cases of lymphadenopathy have been reported in patients using pimecrolimus cream. Treatment with pimecrolimus should be stopped in patients who develop lymphadenopathy in the absence of a clear aetiology or in the presence of acute infectious mononucleosis. Patients should be monitored to ensure that the condition resolves.

Carcinogenicity. Carcinogenicity studies in *animals* and reports of malignancies in patients treated with topical calcineurin inhibitors prompted the FDA to issue an alert about the possible risk and to make recommendations about the appropriate use of topical pimecrolimus and tacrolimus (see under Tacrolimus, p. 1971.2).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies pimecrolimus as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

Alcohol intolerance, described as flushing, rash, burning, itching, or swelling, has occurred rarely after the consumption of alcohol by patients using topical pimecrolimus.

Pharmacokinetics

There is minimal systemic absorption and no accumulation from topical use of pimecrolimus. Studies in *animals* and *in vitro* have found no evidence of metabolism in the skin.

Pimecrolimus is absorbed from the gastrointestinal tract after oral doses, and is about 74 to 87% bound to plasma proteins. It is metabolised in the liver by the cytochrome P450 isoenzyme CYP3A subfamily. About 78% of a single dose is eliminated in the faeces as metabolites and less than 1% as unchanged pimecrolimus. Only about 2.5% of a dose is eliminated in the urine, as metabolites.

References.

1. Van Leent EJM, *et al.* Low systemic exposure after repeated topical application of pimecrolimus (Elidel. SD Z ASM 981) in patients with atopic dermatitis. *Dermatology* 2002; 204: 63–8.
2. Scott G, *et al.* Pharmacokinetics of pimecrolimus, a novel nonsteroid anti-inflammatory drug, after single and multiple oral administration. *Clin Pharmacokinet* 2003; 42: 1305–14.
3. Zollinger M, *et al.* Pimecrolimus: absorption, distribution, metabolism, and excretion in healthy volunteers after a single oral dose and supplementary investigations in vitro. *Drug Metab Dispos* 2006; 34: 765–74.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Elidel; *Austral.*: Elidel; *Austria*: Elidel; *Belg.*: Elidel; *Braz.*: Elidel; *Canad.*: Elidel; *Chile*: Elidel; *China*: Elidel (爱宁达); *Cz.*: Elidel; *Denm.*: Elidel; *Fin.*: Elidel; *Ger.*: Elidel; *Gr.*: Aregen; Elidel; *Hong Kong*: Elidel; *Hung.* Elidel; *India*: Elidel; Pacroma; *Indon.*: Elidel; *Israel*: Elidel *Ital.*: Elidel; *Malaysia*: Elidel; *Mex.*: Elidel; *Neth.*: Elidel; *Norw.* Elidel; *NZ*: Elidel; *Philipp.*: Elidel; *Pol.*: Elidel; *Port.*: Aregen Elidel; *Rus.*: Elidel (Элидел); *S.Afr.*: Elidel; *Singapore*: Elidel† *Spain*: Elidel; Rizan; *Swed.*: Elidel; *Switz.*: Elidel; *Thai.*: Elidel *Turk.*: Elidel; *UK*: Elidel; *Ukr.*: Elidel (Элидел); *USA*: Elidel *Venez.*: Elidel.

Piroctone Olamine (USAN, rINNM)

Piroctona olamina; Piroctoni Olaminum; Пироктон Оламин.

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1*H*)-pyridone compound with 2-aminoethanol (1:1).

$C_{14}H_{23}NO_2.C_2H_7NO$=298.4

CAS — 50650-76-5 (piroctone); 68890-66-4 (piroctone olamine).

UNII — A4V5C6R9FB.

Profile

Piroctone olamine has been used in shampoos for the treatment of dandruff.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Plusgel†; *Braz.*: Soapex; *Fr.*: Charlieu Antipelliculaire†; Evolith DS†; Topicrem Traitement PV†; *Ital.*: Olamin P†; *Mex.*: Betapirox; *Venez.*: Betapirox.

Multi-ingredient Preparations. *Arg.*: Micocert; Micodual; Pitiriax; *Braz.*: Ortosol P; Pityval; Saliker; *Chile*: Anastim; Eucerin Shampoo Anticaspa†; Eucerin Shampoo para el Tratamiento de la Caspa; Foltene Research Anticaspa†; Kerium Anticaspa - Caspa Grasa; Kerium Anticaspa -Caspa Seca; Kerium Anticaspa Intensivo; Micodual; NeoStrata; Node DS†; Pityval; Shampoo Anticaspa†; *Fr.*: Ionax P†; Kelual DS; Kertyol Intensive†; Kertyol Shampooing†; Node DS+; Node DS; Node P†; Novophane DS; Novophane K; Phytheol Force†; Phytosquame†; Pityval†; PSO†; Sebortheane†; *India*: Climdan; *Irl.*: Effaclar AI; *Israel*: Atopiclair; Xclair; *Ital.*: Biophase Shampoo; Biothymus DS; Biothymus DS; Genisol; Nonak; Prurex; Sideck Shampoo Antiforfora; Tricoderm F; *Port.*: Alpha Septol; Biodin Sebo Care†; *Singapore*: Atopiclair; Pedimed Foot Care Cream; *Turk.*: Numis; *UK*: Atopiclair; *USA*: Atopiclair; *Venez.*: Anastim; Kertyol; Node DS; Sensibio DS.

Podophyllum

American Mandrake; May Apple Root; Podófilo; Podofilum; Podoph.; Podophyllum Rhizome; Rizoma de podófilo; Подофилл щитовидный (*Podophyllum peltatum*).

ATC Herb — HA06AB5012 (Podophyllum peltatum: rhizome).
UNII — 5Y42EY85M7 (Podophyllum peltatum); 25713A4VP3 (Podophyllum peltatum root);

Pharmacopoeias. In *US*.

USP 36: (Podophyllum). The dried rhizomes and roots of *Podophyllum peltatum* (Berberidaceae). It yields not less than 5% of resin. It has a slight odour.

Indian Podophyllum

Ind. Podoph.; Indian Podophyllum Rhizome; Podófilo indio; Подофилл гималайский (*Podophyllum emodi*).

Description. The dried fruits or rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*) (Berberidaceae).

Podophyllum Resin

Podofilino; Podoph. Resin; Podophylli Resina; Podophyllin; Resina de podófilo; Подофиллин.

CAS — 8050-60-0.
ATC Herb — HD06BB5001 (Podophyllum peltatum: resin); HA06AB5011 (Podophyllum peltatum: resin).
UNII — 16902YVY2B.

Pharmacopoeias. In *Int.* and *US* (both from podophyllum only). In *Br.* from Indian podophyllum.

BP 2014: (Podophyllum Resin). The resin obtained from the rhizomes and roots of *Podophyllum hexandrum* (*P. emodi*). It contains not less than 50% of total aryltetralin lignans, calculated as podophyllotoxin.

An amorphous powder, varying in colour from light brown to greenish-yellow or brownish-grey masses, with a characteristic odour; caustic. On exposure to light or to temperatures above 25 degrees it becomes darker in colour.

Partly soluble in hot water but precipitated again on cooling; partly soluble in chloroform, in ether, and in dilute ammonia solution. Protect from light.

USP 36: (Podophyllum Resin). The powdered mixture of resins extracted from podophyllum (the rhizomes and roots of *Podophyllum peltatum*) by percolation with alcohol and subsequent precipitation with acidified water. It contains not less than 40% and not more than 50% of hexane-insoluble matter.

An amorphous caustic powder, varying in colour from light brown to greenish-yellow. On exposure to light or to temperatures above 25 degrees it becomes darker in colour.

Soluble in alcohol with a slight opalescence; partially soluble in chloroform and in ether. A solution in alcohol is acid to litmus. Store in airtight containers. Protect from light.

Podophyllotoxin *(BAN)*

Podofilotoxina; Podofilox (USAN); Podofyllotoksiini; Podofyllotoxin; Podophyllotoxinum; Подофиллотоксин.

(5*R*,5a*R*,8a*R*,9*R*)-5,5a,6,8,8a,9-Hexahydro-9-hydroxy-5-(3,4,5-trimethoxyphenyl)furo[3′,4′:6,7]naphtho[2,3-*d*]-1,3-dioxol-8-one.

$C_{22}H_{22}O_8$=414.4

CAS — 518-28-5.
ATC — D06BB04.
ATC Vet — QD06BB04.
UNII — L36H5OF353.

Uses and Administration

Podophyllum resin and podophyllotoxin have an antimitotic action and are used mainly as topical treatments for anogenital warts (condylomata acuminata). Podophyllum resin and podophyllotoxin may be used on external genital and perianal warts; podophyllum resin may also be used on urethral meatus warts. However, neither of these compounds should be used to treat warts on mucous membranes, including vaginal, cervical, intra-urethral, intra-anal, and rectal warts.

Podophyllum resin is usually formulated in compound benzoin tincture in strengths of 15% Indian podophyllum resin or 10 to 25% American podophyllum resin. Lower concentrations of American podophyllum resin in alcoholic solutions have been used. The solution is left on the warts for 1 to 4 hours, and then washed off. Only a small area or number of warts should be treated at any one time and care must be taken to avoid application to healthy tissue. This procedure is carried out once a week for up to 3 to 6 weeks. Preparations containing podophyllotoxin 0.5% in alcohol or alcoholic gel or podophyllotoxin 0.15% cream are used similarly. They are applied twice daily for 3 days but not washed off. Treatment may be repeated at weekly intervals for up to a total of 4 or 5 weeks of treatment. Podophyllum resin is also used with other keratolytics for the removal of plantar warts.

Although podophyllum resin and podophyllotoxin preparations are generally not used in children, see below.

When taken orally podophyllum resin is highly irritant to the intestinal mucosa and produces violent peristalsis resulting in a drastic purging action. It has been superseded by less toxic laxatives.

Homoeopathy

Podophyllum has been used in homoeopathic medicines under the following names: Podoph pelt; Podophyllum peltatum.

Podophyllum resin has been used in homoeopathic medicines under the following names: Podophyllinum.

Administration in children. The use of podophyllum resin and podophyllotoxin preparations in children is generally avoided because of the potential for severe local irritation and systemic toxicity. Nonetheless, some podophyllum resin-containing preparations are licensed in children for the treatment of plantar warts. Also, podophyllotoxin has been used for the treatment of symptomatic, persistent anogenital warts in children.[1] The *BNFC* suggests that, although not licensed for use in children, podophyllotoxin preparations may be used in regimens similar to those used in adults (see above) in children 2 years of age and older who are able to cooperate with treatment.

1. Bellew SG, *et al.* Childhood warts: an update. *Cutis* 2004; 73: 379–84.

Anogenital warts. Podophyllum preparations are one of the treatment choices for anogenital warts caused by human papillomavirus infection (condylomata acuminata) (p. 1689.3). Podophyllum resin preparations have traditionally been applied by a healthcare provider because of the potential local and systemic toxicity associated with inappropriate or excessive use.[1] However, podophyllotoxin may be more effective[2,3] and less toxic[2] than podophyllum resin, and is suitable for self-treatment by the patient.[1,4]

1. CDC. Sexually transmitted diseases treatment guidelines, 2010. *MMWR* 2010; 59 (RR-12): 1–110. Correction. *ibid.* 2011; 60: 18. [dose] Also available at: http://www.cdc.gov/STD/treatment/2010/STD-Treatment-2010-RR5912.pdf (accessed 02/02/11)
2. von Krogh G, Longstaff E. Podophyllin office therapy against condyloma should be abandoned. *Sex Transm Infect* 2001; 77: 409–12.
3. Lacey CJN, *et al.* Randomised controlled trial and economic evaluation of podophyllotoxin solution, podophyllotoxin cream, and podophyllin in the treatment of genital warts. *Sex Transm Infect* 2003; 79: 270–5.
4. von Krogh G, *et al.* European Course on HPV Associated Pathology (ECHPV). European guideline for the management of anogenital warts. *Int J STD AIDS* 2001; 12 (suppl 3): 40–7. Also available at: http://www.iustl.org/sti-information/pdf/guidelines.pdf (accessed 27/09/07)

Adverse Effects

Podophyllum is very irritant, especially to the eyes and mucous membranes. It can also cause severe systemic toxicity after ingestion or topical application, which is usually reversible but has been fatal. Symptoms of toxicity include nausea, vomiting, abdominal pain, and diarrhoea; there may be thrombocytopenia, leucopenia, renal failure, and hepatotoxicity. Central effects are delayed in onset and prolonged in duration and include acute psychotic reactions, hallucinations, confusion, dizziness, stupor, ataxia, hypotonia, seizures, and coma. EEG changes may persist for several days. Peripheral and autonomic neuropathies develop later and may result in paraesthesias, reduced reflexes, muscle weakness, tachycardia, apnoea, orthostatic hypotension, paralytic ileus, and urinary retention. Neuropathy may persist for several months.

Poisoning. Reports and reviews of podophyllum toxicity.[1-7] A few of the cases followed consumption of herbal preparations containing podophyllum or the related plant bajiaolian (*Dysosma pleianthum*). Death has occurred after ingestion of 10 g of podophyllum.

1. Cassidy DE, *et al.* Podophyllum toxicity: a report of a fatal case and a review of the literature. *J Toxicol Clin Toxicol* 1982; 19: 35–44.
2. Dobb GJ, Edis RH. Coma and neuropathy after ingestion of herbal laxative containing podophyllin. *Med J Aust* 1984; 140: 495–6.
3. Holdright DR, Jahangiri M. Accidental poisoning with podophyllin. *Hum Exp Toxicol* 1990; 9: 55–6.
4. Tomczak RL, Bake DH. Near fatal systemic toxicity from local injection of podophyllin for pedal verrucae treatment. *J Foot Surg* 1992; 31: 36–42.
5. Kao W-F, *et al.* Podophyllotoxin intoxication: toxic effect of bajiaolian in herbal therapeutics. *Hum Exp Toxicol* 1992; 11: 480–7.
6. Chan TYK, Critchley JAJH. Usage and adverse effects of Chinese herbal medicines. *Hum Exp Toxicol* 1996; 15: 5–12.
7. Chu CC, *et al.* Sensory neuropathy due to bajiaolian (podophyllotoxin) intoxication. *Eur Neurol* 2000; 44: 121–3.

Precautions

The risk of systemic toxicity after topical application of podophyllum is increased by the treatment of large areas with excessive amounts for prolonged periods, by the treatment of friable, bleeding, or recently biopsied warts, and by inadvertent application to normal skin or mucous membranes.

Podophyllum should not be used during pregnancy or breast feeding. There are few reports of use during pregnancy and a teratogenic risk cannot be ruled out. Adverse systemic effects in the mother would also be undesirable during pregnancy, and there are other non-drug treatments available for the treatment of anogenital warts. It is unknown whether podophyllum is distributed into breast milk.

Handling. Podophyllum resin is strongly irritant to the skin, eyes, and mucous membranes and requires careful handling.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies podophyllotoxin as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Podoxin; *Austral.*: Condyline; Wartec; *Austria*: Condylox; *Belg.*: Wartec; *Braz.*: Wartec; *Canad.*: Condyline; Podofilm; Wartec; *China*: Condylox (偎定来); Podofilm (尤力青); Wartec (华特); You Tuo Xin (尤脱欣); *Cz.*: Wartec; *Denm.*: Condyline; Wartec; *Fin.*: Condyline; Wartec; *Fr.*: Condyline; *Ger.*: Condylox; Wartec; *Gr.*: Podofilox; Wartec; *Hong Kong*: Podofilm; Wartec; *Hung.*: Condyline; Wartec; *India*: Condyline; *Irl.*: Condyline; Warticon; *Israel*: Condylox; *Ital.*: Condyline; Wartec; *Mex.*: Podofilia; Vipodo; Wartec; *Neth.*: Condyline; Wartec; *Norw.*: Condyline; Wartec; *NZ*: Condyline; Wartec; *Pol.*: Condyline; Wartec; *Port.*: Condylina†; *Rus.*: Condyline (Кондилин); Wartec (Вартек); *S.Afr.*: Wartec; *Singapore*: Podofilm; Wartec; *Spain*: Wartec; *Swed.*: Condyline; Wartec; *Switz.*: Condyline; Warix; *Turk.*: Podofilm; *UK*: Condyline; Warticon; *Ukr.*: Wartec (Вартек); *USA*: Condylox; Pod-Ben-25; Podocon; Podofin.

Multi-ingredient Preparations. *Austral.*: Posalfilin†; *Canad.*: Canthacur-PS; Cantharone Plus; *Ger.*: Unguentum lymphaticum†; *Hong Kong*: P-Podofilm†; *Irl.*: Posalfilin; *Neth.*: Diarrheel S; *NZ*: Posalfilin; *Port.*: Doce Alivio; *S.Afr.*: Posalfilin†; *Spain*: Alofedina; *Turk.*: Canthacur-PS; *UK*: Posalfilin†; *Venez.*: Linfoderm.

Homoeopathic Preparations. *Austral.*: IBS Eze; Stomach Calm; *Austria*: Daram; Zahnkugelchen; *Canad.*: Carduus Plex†; Diarrex: Indigestion†; Vegetal Tonic; *Fr.*: Aloe Compose; Basilicum Complexe No 96; Bilinum Complexe No 113; Billerol; Diaralia; Hepatopan†; L 114; Ricinus Compose; Tonique Vegetal; *Ger.*: Cefaspasmon N†; Chola-Plantin N†; *Rus.*: Berberis-Plus (Берберис-Плюс); *Switz.*: Diarrheel S; *Ukr.*: Choledius (Холедиус).

Pharmacopoeial Preparations
BP 2014: Compound Podophyllin Paint;
USP 36: Podophyllum Resin Topical Solution.

Polyphloroglucinol Phosphate

Polifloroglucinol, fosfato de; Polyphloroglucin Phosphate; Полифлороглюцина Фосфат.

Poly(benzene-1,3,5-triol mono(dihydrogen phosphate)).

$(C_6H_7O_5P)_n$

CAS — 51202-77-8.

Profile

Polyphloroglucinol phosphate has an inhibitory effect on hyaluronidase and has been applied topically in the treatment of wounds and pruritic skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Dealyd.

Polyurethane Foam *(USAN)*

Полиуретановая Пена; Пенополиуретан.
CAS — 9009-54-5.

Profile

Polyurethane foam is a urethane polymer that is used in wound dressings.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Allevyn; Opsite; *Belg.*: Allevyn; Askina Transorbent†; Biatain; Combiderm; Duoderm E; Mepilex; Permafoam; Tegaderm Foam; Tielle; *Canad.*: Tegaderm Foam; *Chile*: Epi Foam; *Fr.*: Allevyn; Clip Blessures†; Clip Derm†; Clip Strip†; Opsite; Optiskin†; Permafoam; Suprasorb; Tielle†; *Ger.*: Allevyn; Biatain Ag; Biatain-Ibu; Biatain; DracoFoam; Opsite; *Irl.*: Allevyn; *Ital.*: Allevyn; Bioclusive; Cutinova Hydro; Opsite Flexigrid; Suprasorb F, M, P; *S.Afr.*: Opsite; *UK*: Allevyn; Cutinova; Lyofoam; Opsite.

Multi-ingredient Preparations. *Ital.*: Biopatch; Silverdres.

Prezatide Copper Acetate *(USAN, rINN)*

Acetato de prezatida cúprica; Acetato de prezatida de cobre; PC-1020 (prezatide copper); Prezatida cúprica, acetato de; Prézatide Cuprique, Acétate de; Prezatidi Cuprici Acetas; Презатида Меди Ацетат.
Hydrogen [N^2-(*N*-glycyl-L-histidyl)-L-lysinato][N^2-(*N*-glycyl-L-histidyl)-L-lysinato(2−)]cuprate(1−) diacetate.
$C_{28}H_{46}CuN_{12}O_8.2C_2H_4O_2$=862.4
CAS — 130120-57-9.
UNII — A3LEI4P1NB.

Profile

Prezatide copper acetate is a copper-containing tripeptide that is used topically as a wound-healing agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Mex.*: Iamin†; *USA*: Iamin Hydrating Gel.

Pyrithione Zinc *(BAN, USAN, rINN)*

Cinko Piritiona; Piritiona cíncica; Piritiona de zinc; Pyrithione Zincique; Pyrithionum Zincicum; Zinc 2-Pyridinethiol 1-Oxide; Zinc Pyridinethione; Пиритион Цинк.
Bis[1-hydroxypyridine-2(1*H*)-thionato]zinc.
$C_{10}H_8N_2O_2S_2Zn$=317.7
CAS — 13463-41-7.
ATC — D11AX12.
ATC Vet — QD11AX12.
UNII — R953O2RHZ5.

Profile

Pyrithione zinc has bacteriostatic and fungistatic properties. It is used similarly to selenium sulfide (p. 1720.1) in usual concentrations of 1 to 2% in the control of seborrhoeic dermatitis and dandruff (p. 1689.1). It is an ingredient of some proprietary shampoos. It has also been used in the treatment of pityriasis versicolor.

Pyrithione magnesium has also been used.

Effects on the nervous system. Peripheral neuritis with paraesthesia and muscle weakness in a patient was associated with the prolonged use of a shampoo containing pyrithione zinc 2%.[1] The muscle weakness had disappeared 3 months after stopping the shampoo and 2 years later the paraesthesia had improved by about 75%.

Studies in *animals* had found signs of neurotoxicity after oral doses of pyrithione zinc but whereas absorption after topical application was found to be 13% for pyrithione sodium it was less than 1% for pyrithione zinc.[2]

1. Beck JB. Zinc pyrithione and peripheral neuritis. *Lancet* 1978; i: 444.
2. Parekh CK. Zinc pyrithione and peripheral neuritis. *Lancet* 1978. i: 940.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aeroseb; Amenite Cap; Antiminth; Dermazinc Hairplus; Min Huil; Molnia; Skin-Cap; *Austral.*: Dan-Gard†; Dandruff Control Pert 2 in 1; *Austria*: Desquaman; *Braz.*: ZN Shampoo; *Canad.*: Active Control†; Actrol†; American Crew Classic Axe Armour; Axe Freeze†; Biolage Scalptherapie; Brylcreem Anti-Dandruff†; Chill Blast†; Dan-Gard; Dandruff Conditioner; Dandruff Shampoo; Dandruff; Denorex Everyday; Dermazinc; Essaim†; Fructis Anti-Dandruff; Head & Shoulders; Herbal Essences No Flakin Way Antidandruff†; Herbal Shampoo and Scalp Treatment†; Intense Clear; KMS; Life Dandruff; Normal Dandruff Treatment†; Out of Africa†; Pantene Anti-Dandruff†; Pert Plus; Power Clear†; Purete†; Retaliate; Rodan & Fields Proactiv Antidandruff†; Satinique Dandruff Control; Scalp Relief; Selsun Blue Anti-Dandruff; Shampoo Control; Shampooing Anti-Pelliculaire; Sprayzinc; T/Gel Daily Control; Vive Men†; Zinc Zap; ZNP†; *Chile*: Biolane; DHS Zinc; Skin Cap; ZNP†; *China*: Skin-Cap (适令可); *Fr.*: Skin Cap; ZNP†; *Gr.*: Daohair-S; Desquaman; *Hung.*: Freederm pH Balance Shampoo; Freederm Zinc Shampoo; *Indon.*: Blue Cap; Blue Cap; Blue Cap; *Israel*: Desquaman; *Ital.*: Rivescal ZPT; SDE Zinc ZNP; *Mex.*: Pirimed; ZNP; *Port.*: ZP Dermil; *Rus.*: Cinocap (Цинокап); Freederm Zinc (Фридерм Цинк); Skin-Cap (Скин-Кап); *Spain*: Zincation†; *Turk.*: Zetion; Zintion; *Ukr.*: Psoricap (Псорикап); *USA*: DermaZinc; DHS Zinc; Head & Shoulders; Noble Formula; Skin Cure; Zincon; ZNP; *Venez.*: Albepir; Blue Caps; Pirimed.

Multi-ingredient Preparations. *Arg.*: Aeroseb; Zinc-S Plus; *Austral.*: Fongitar†; *Braz.*: Fisohex II; *Canad.*: Herbal Multi-Tar Plus; Mild Multi-Tar Plus; Multi-Tar Plus†; Regular Multi-Tar Plus; X-Seb Plus; Z-Plus; *Chile*: Node DS†; *Cz.*: Polytar AF; *Fr.*: Kelual DS; Node DS+; Node DS; Node P†; Novophane DS; Novophane K; *Hong Kong*: Fongitar; Multi-Tar†; *Hung.*: Polytar AF†; Squa-med; *India*: Apodruff; Clinhair; Danclear; Dancure; Emvate; Everzple; Flakefree; Fungicide; Hyphoral; Kekona; Ketosis; Ketz; Koiz; KTC; Nazcare; Nazz; Nuforce Shampoo; Ocona-Z; Scalpe; *Ital.*: Biothymus DS; Keto Z; Ketomousse; Kevis; *Malaysia*: Ketoplus; *Philipp.*: Fongitar; Scalpex; *Pol.*: Polytar AF; *Port.*: Alpha Septol; Fongitar; *Rus.*: Keto Plus (Кето Плюс); *S.Afr.*: Fongitar; *Singapore*: Fongitar; *Spain*: Zincation Plus; *Switz.*: Sebo-Soufrol†; Squa-med; *Thai.*: Fongitar†; *Turk.*: Pirdolin; Seboreks; Sedolin†; *UK*: Polytar AF†; *Ukr.*: Keto Plus (Кето Плюс); *USA*: Denorex Dual Force; X-Seb Plus; Xolegel Duo; *Venez.*: Node DS; Pelset Plus.

Pyrogallol

1,2,3-Bencenotriol; Pirogálico, ácido; Pirogalol; Pyrogallic Acid; Pyrogallolum; Пирогаллол.
Benzene-1,2,3-triol.
$C_6H_6O_3$=126.1
CAS — 87-66-1.
UNII — 01Y4A2QXY0.

Pharmacopoeias. In *Fr.* and *Pol.*

Profile

Pyrogallol was formerly used topically in the treatment of psoriasis and parasitic skin diseases, but application over large areas or denuded surfaces is dangerous and may produce systemic effects similar to phenol poisoning (see p. 1764.2); methaemoglobinaemia, haemolysis, and kidney damage may also occur.

Pyrogallol stains the skin and hair black.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Pyrogallic.

Pyroxylin *(rINN)*

Algodão-Polvora; Algodón pólvora; Cellulose Nitrate; Celulosa decanítrica; Colloxylinum; Fulmicoton; Gossypium Collodium; Kollodiumwolle; Nitrato de celulosa; Piroxilina; Pyroxyline; Pyroxylinum; Soluble Guncotton; Пироксилин.
CAS — 9004-70-0.
UNII — KYR8BR2X6O.

Pharmacopoeias. In *Br.*, *Jpn*, *Pol.*, and *US.*

BP 2014: (Pyroxylin). A nitrated cellulose obtained by the action of a mixture of nitric and sulfuric acids on wood pulp or cotton linters that have been freed from fatty matter. It must be damped with not less than 25% of isopropyl alcohol or of industrial methylated spirit. White or almost white cuboid granules or fibrous material resembling absorbent cotton but harsher to the touch and more powdery. It is highly flammable. Soluble in acetone and in glacial acetic acid. Store in well-closed containers, loosely packed, protected from light, and at a temperature not exceeding 15 degrees, remote from fire. The container should be suitably designed to disrupt should the internal pressure reach or exceed 1400 kPa. The amount of damping fluid must not be allowed to fall below 25% w/w; should this happen, the material should be either rewetted or used immediately for the preparation of Collodion.

USP 36: (Pyroxylin). Pyroxylin is obtained by the action of a mixture of nitric and sulfuric acids on cotton and consists chiefly of cellulose tetranitrate ($C_{12}H_{16}N_4O_{18})_n$. It occurs as a light yellow, matted mass of filaments resembling raw cotton but harsher to the touch. It is highly flammable. Store loosely packed, protected from light. When kept in well-closed containers and exposed to light, it decomposes with the evolution of nitrous vapours, leaving a carbonaceous residue.

Profile

Pyroxylin is used in the preparation of collodions which are applied to the skin for the protection of small cuts and abrasions. Collodions are also used as vehicles for the application of drugs when prolonged local action is required.

Handling. Dry pyroxylin is explosive and sensitive to ignition by impact or friction and should be handled carefully.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Callicida; *Neth.*: Duofilm; *UK*: Dispello; *Venez.*: Kayivis.

Pharmacopoeial Preparations
BP 2014: Collodion; Flexible Collodion;
USP 36: Collodion; Flexible Collodion.

Resorcinol

m-Dihidroxibenceno; *m*-Dihydroxybenzene; Dioxybenzolum; Resorcin; Resorcina; Résorcinol; Resorcinolum; Resorsinoli; Rezorcin; Rezorcinolis; Rezorcynol; Резорцинол.
Benzene-1,3-diol.
$C_6H_6O_2$=110.1
CAS — 108-46-3.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.
UNII — YUL4LO94HK.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US.*

Ph. Eur. 8: (Resorcinol). Colourless or slightly pinkish-grey crystals or crystalline powder. M.p. 109 degrees to 111 degrees. It becomes red on exposure to air and light. Very soluble in water and in alcohol. Protect from light.

USP 36: (Resorcinol). White or practically white, needle shaped crystals or powder with a faint characteristic odour M.p. 109 degrees to 111 degrees. It acquires a pink tint on exposure to air and light. Soluble 1 in 1 of water and of alcohol; slightly soluble in chloroform; freely soluble in ether and in glycerol. A 5% solution in water is neutral or acid to litmus. Protect from light.

Incompatibility. Resorcinol is incompatible with ferric salts.

Resorcinol Monoacetate

Acetato de resorcina; Resorcin Acetate; Resorcinol, monoacetato de; Резорцинола Моноацетат.
3-Acetoxyphenol.
$C_8H_8O_3$=152.1
CAS — 102-29-4.
ATC — D10AX02; S01AX06.
ATC Vet — QD10AX02; QS01AX06.
UNII — YL6O37RD1S.

Pharmacopoeias. In *US.*

USP 36: (Resorcinol Monoacetate). A pale yellow or amber, viscous liquid with a faint characteristic odour. Sparingly soluble in water; soluble in alcohol and in most organic solvents. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Uses and Administration

Resorcinol has keratolytic properties and has been used, usually with sulfur, in topical preparations for the treatment of acne (p. 1682.2) and seborrhoeic skin conditions (p. 1689.1), although other treatments are generally preferred.

Resorcinol has also been used in preparations for the treatment of anorectal disorders often complexed with bismuth compounds (see Haemorrhoids, p. 1808.1).

Resorcinol monoacetate has been used similarly but may provide a milder action with a longer duration.

Dentistry. Resorcinol powder added incrementally to a few drops of formaldehyde 40% solution to saturation and polymerised using 1 or 2 drops of sodium hydroxide 10% solution produces a hard red material, known as "Russian Red". This resin has been used in dentistry in eastern Europe, Russia, and China. Zinc oxide or barium sulfate is

often added to the mixture before polymerisation to make it radio-opaque.[1]

1. Schwandt NW, Gound TG. Resorcinol-formaldehyde resin "Russian Red" endodontic therapy. *J Endod* 2003; **29**: 435–7.

Adverse Effects, Treatment, and Precautions

Resorcinol is a mild irritant and may result in skin sensitisation. It should not be applied to large areas of the body, for prolonged periods, or in high concentrations, especially in children, as it is absorbed through intact skin as well as broken skin and may interfere with thyroid function or produce methaemoglobinaemia. Resorcinol may produce hyperpigmentation in patients with dark skins and may darken light-coloured hair. Systemic toxic effects of resorcinol are similar to those of phenol and are treated accordingly (see p. 1764.3) but convulsions may occur more frequently.

Abnormal coloration. Resorcinol could cause green discoloration of the urine.[1]

1. Karlstrand J. The pharmacist and the ostomate. *J Am Pharm Assoc* 1977; **NS17**: 735–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Dermobarrina; *USA*: Castel.

Multi-ingredient Preparations. *Arg.*: Acnoxin; Astriluge; Bifena; Callicida; Control Acne; Cutidermin Bebe Polvo†; Dermacne; Dermo Vagisil Crema; Ecnagel E; Ecnagel; Farmigras; Merbenloc; Nemegel; Pinklot; Suffisance; Ukase Dermo; Xicanil Control†; *Austral.*: Eskamel†; *Braz.*: Pantevit; *Canad.*: Acnomel†; Clearasil Acne Control†; Clearasil Acne Cream†; Clearasil Stay-clear†; Hemo-Pict†; Lanacane Medicated Cream; Mazon Medicated Cream; Sebo Concept D/A; Vagisil; *Chile*: Dermac Crema; *Fr.*: Anaxeryl; Bain de Bouche Lipha†; Gelictar Port†; Nestosyl; Osmotol; Paracamf; Paradentose†; Squaphane S; Synthol; *Gr.*: Creme Phyllis de Jeunesse; Neo Akmine; Rysolone; *Hong Kong*: Acne-Aid†; *Hung.*: Glycosept; *Indon.*: Bioacne; Rosal; Verile; *Irl.*: Anusol-HC; *Israel*: Pitrisan†; *Ital.*: Blefarolin; Fucsina Fenica; Labocaina; *Malaysia*: Acne-Aid†; *Mex.*: Acnomel; Axel; Dermac; Dermocare; Dermoscalp; Jabon del Tio Nacho; Shampoo del Tio Nacho†; *NZ*: Lanacane; *Pol.*: Afronis; Hemorectal; *Port.*: Resodermil†; *Rus.*: Fucaseptol (Фукасептол); Pucorcin (*Фукорцин*); Neo-Anusol (*Нео-анузол*); *S.Afr.*: Anugesic†; Eskamel†; *Singapore*: Acne Clear; Acne-Aid†; Castellani's Paint; *Spain*: Dermomycose Liquido; Milrosina; Resorborina; *Switz.*: Clabin; Eau Precieuse; Lotio decapans; *Thai.*: Anusol†; Zema; *Turk.*: Buco Bleu; Pilo Cura; *USA*: Acnomel; Bensulfoid; Bicozene†; Castaderm; Dermarest; Fungi-Nail; Heal Aid Plus; RA Lotion; Rezamid; Sulforcin; Unguentine Maximum Strength; Vagisil; *Venez.*: Klenyl.

Homoeopathic Preparations. *Canad.*: ClearAc Cleanser†.

Pharmacopoeial Preparations
BPC 1973: Magenta Paint;
USP 36: Carbol-Fuchsin Topical Solution; Compound Resorcinol Ointment; Resorcinol and Sulfur Topical Suspension.

Retinaldehyde

Retinal; Retinene; Vitamin A Aldehyde; Ретинальдегид.
$C_{20}H_{28}O$=284.4
CAS — 116-31-4.
UNII — RR725D715M.

Profile

Retinaldehyde is a derivative of vitamin A (p. 2098.3) that has been used in preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Ystheal; *Chile*: Ystheal.

Multi-ingredient Preparations. *Arg.*: Diacneal; Diroseal; Eluage; *Chile*: Diacneal; Diroseal; *Fr.*: Diroseal†; *Venez.*: Diacneal.

Salicylic Acid

Acide salicylique; Acido Ortoxibenzoico; Acidum salicylicum; Kwas salicylowy; Kyselina salicylová; Salicílico, ácido; Salicilo rūgštis; Salicylsäure; Salicylsyra; Salisilik Asit; Salisyylihappo; Salizylsäure; Szalicilsav; Салициловая Кислота.
2-Hydroxybenzoic acid.
$C_7H_6O_3$=138.1
CAS — 69-72-7.
ATC — D01AE12; S01BC08.
ATC Vet — QD01AE12; QS01BC08.
UNII — O414PZ4LPZ.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Salicylic Acid). White or colourless acicular crystals or a white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol; sparingly soluble in dichloromethane. Protect from light.

USP 36: (Salicylic Acid). White crystals, usually in fine needles or a white, fluffy, crystalline powder. The synthetic form is white and odourless but if prepared from natural methyl salicylate it may have a slightly yellow or pink tint, and a faint, mint-like odour. Soluble 1 in 460 of water, 1 in 15 of boiling water, 1 in 3 of alcohol, 1 in 45 of chloroform, 1 in 3 of ether, and 1 in 135 of benzene.

Uses and Administration

Salicylic acid has **keratolytic** properties and is applied topically in the treatment of hyperkeratotic and scaling skin conditions such as dandruff and seborrhoeic dermatitis (p. 1689.1), ichthyosis (p. 1685.1), psoriasis (p. 1688.1), and acne (p. 1682.2). Preparations usually contain between 2 and 6% salicylic acid, but a wider range of concentrations has been used. It is often used with other drugs, notably coal tar.

Preparations containing up to 60% salicylic acid have been used as a **caustic** for the removal of plantar warts (p. 1689.3), corns, or calluses; surrounding healthy skin should be protected (see below).

Salicylic acid also possesses **fungicidal** properties and is used topically in the treatment of dermatophyte skin infections (see p. 568.1); propyl salicylate and bromosalicylic acid have been used similarly.

Zinc salicylate has been used similarly to salicylic acid in the treatment of seborrhoeic dermatitis and acne.

Adverse Effects and Precautions

Salicylic acid is a mild irritant and application of salicylic acid preparations to the skin may cause dermatitis. Preparations containing high concentrations of salicylic acid can cause skin ulceration or erosion; healthy skin surrounding warts, corns, and calluses should be protected with soft paraffin or specially designed plasters when such preparations are being used. Salicylic acid should be used with care on the extremities of patients with impaired peripheral circulation or diabetes; caution has also been suggested if caustic preparations are used in patients with significant peripheral neuropathy. The drug is readily absorbed through the skin, and symptoms of acute systemic salicylate poisoning (see Aspirin, p. 24.2) have been reported after excessive use; deaths have occurred, mainly in children. To minimise absorption after topical application salicylic acid should not be used for prolonged periods, in high concentrations, on large areas of the body, or on inflamed or broken skin. Contact with mouth, eyes, and other mucous membranes should be avoided. In the UK, the MHRA has recommended that topical oral pain relief preparations containing salicylates should not be used in children under 16 years of age (for details, see Reye's Syndrome, p. 39.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Callicida; Callicida; Duofilm; Duoforte; Effaclar K; Koal; Neo A-V; Renovate; Salpad; Verrutopic AS; Verrutrix; *Austral.*: Clearasil Blackhead Control; Clearasil DailyClear; Clearasil Medicated Wipes†; Clearasil Ultra Overnight; Clearasil Ultra Rapid; Duofilm; Egozite Cradle Cap; Ionil; John Plunketts Sunspot Cream; *Austria*: Squamasol; *Belg.*: Anticors Diable Vert†; Duofilm; Sicombyl; *Braz.*: A Curitybina; Clean & Clear Gel Secativo; Clean & Clear Hidratante; Clean & Clear Locao Adstringente; Ionil; Kalloplast; Neutrogena Antiacne; *Canad.*: Acnopur†; Almay Clear Complexion†; Artistry Blemish Control†; Aveda Balancing; Avon Clearskin Invisible Blemish Corrector†; Avon Clearskin Purifying Gel Cleanser†; Blemish Control; Carnation; Clearasil Cleanser†; Dermarest; Duofilm; Duoforte; Formula P6†; Medicated Callus Removers†; Medicated Corn Removers†; Neutrogena Acne Wash; Neutrogena Clear Pore†; Neutrogena T/Gel Conditioner†; Noxzema Triple Clean†; Occlusal†; pHisoDerm Acne Mask†; Scholl 2-Drop Corn Remedy; Scholl Callus Remover; Scholl Corn Remover; Sebcur; Sensitive Skin Facial Astringent†; Shiseido Pureness Anti-Shine†; Soluver Plus; Soluver; Trans-Plantar†; Trans-Ver-Sal†; X-Seb; Zap-It†; *Chile*: DHS Sal; Duoplant Gel; Eucerin Piel Grasa†; Eucerin Reductor de Sebo/Grasa; Mediklin; Neutrogena Deep Clean Limpiador Facial; Neutrogena Gel Control Brillo†; Neutrogena Linea Acne†; Neutrogena T/Gel Acondicionador; Quitacallos; *Cz.*: Callous†; Sophtal-POS N; Spofaplast†; Urgocor; Verruca Removal†; *Fin.*: Cornina Hansaplast; *Fr.*: Ciella; Coricide le Diable; Feuille de Saule; Ikeriane; Pommade Mo Cochon; Sanitos; Septisol†; Sophtal; Transvercid; Tricosteril Coripel†; Urgocor†; *Ger.*: Aknefug-liquid; Collomack; Gehwol Huhneraugen-Pflaster extra stark; Gehwol Schalpaste; Gothaplast Hornhautpflaster; Gothaplast Huhneraugenpflaster; Lygal Kopfsalbe N†; Psorimed; Schrundensalbe Dermi-cyl; Sophtal-POS N; Squamasol; Urgocor†; Verrucid; *Gr.*: Abadasol†; Adaptoplast; Apsoderm; Asalid; Astemil; Callifugo; Fungiheal; Hansaplast Callous; Opsor; Opsorad; Psorimed; Salicyd; Salipsor; Saronic; Solimed; Zino; *Hong Kong*: Duofilm; Egozite Cradle Cap; *Hung.*: Seal & Heal; *India*: Dersol; Eremis; Keracnyl; *Indon.*: Topix†; Yodsaben†; *Irl.*: Acnisal; Callous Removal Pads; Carnation; Compound W†; Corn Removal Pads; Corn Removers; Occlusal; Pickles; Soft-Corn†; Thwart; Vericaps†; Verrugon; Wartex; *Israel*: Carnation; Clearex for Sensitive Skin; Salikaren; Scholl Corn/Callous Removers; Trans-Ver-Sal; *Ital.*: Keranon; Salicil; Trans-Ver-Sal; *Malaysia*: Clearasil 3 in 1 Deep Cleansing Wash†; Clearasil Ice Wash†; Clearasil Ultra Deep Pore†; Clearasil; Egozite Cradle Cap; Ellgy Corns & Warts; Palmer's Skin Success Acne Medication; *Mex.*: Duoplant; Excelsior; Ionil Plus†; Trans-Ver-Sal; *Mon.*: Antalyre; *Neth.*: Formule W; Psorimed†; *NZ*: Duofilm; Egozite Cradle Cap; *Philipp.*: Ionil†; Wart-Off†; *Pol.*: Callous; Corn and Callous; Corn; Keratolysin†; Masc przeciw Odciskom i Zgrubieniom Skory; Saliderm; Seal & Heal; Soft Corn; Urgo Cor†; *Port.*: Calicida Moreno; Transvercid; Urgocor; Verrufilm; *Rus.*: Urgocor Coricide (*Ургокор Мозолный*); *S.Afr.*: Compound W†; Cross Brand Corn Plasters†; Emzaclear; Freezone†; Jiffy Medi+ Plus†; Piccadilly Foot Ointment; SB Unola Corn Remover†; Trans-Ver-Sal†; Yalta Corn Salve†; *Singapore*: Anti-White Spot; Centa Skin; Clearasil 3 in 1; Clearasil Deep Cleansing; Clearasil Ice Wash; Clearasil Oil Free Gel Wash; Clearasil Skin Perfecting Wash; Clearasil Ultra Acne Clearing; Clearasil Ultra Deep Pore; Clearasil Ultra Rapid Action; Clearasil Ultra Spot Clearing Scrub; Duofilm; FST; Panau Salap; Pineapple Brand Lotion; Senkon White Spot; Toh Skin; White Spot; *Spain*: Callicida Grast†; Callicida Kendu; Callicida Salve†; Callofin†; Unguento Morry; Urgocall†; Verrupatch; Verruplan; *Swed.*: Salsyvase; *Switz.*: Scholl Warzenfilm†; Wurzelitod; *Turk.*: Nasiral; Salsil; Scholl Callous†; *UK*: Acnisal; Carnation; Clearasil Double Action Pads; Compound W; Occlusal; Pickles Foot Ointment; Scholl Callus Removal; Scholl Corn Removal; Scholl Verucca Removal; SCR; Snufflebabe Cradle Cap; Verrugon; Wartex; *USA*: Clearasil Clearstick; Compound W; Dr Scholl's Callus Removers; Dr Scholl's Clear Away; Dr Scholl's Corn Removers; Dr Scholl's Corn/Callus Remover; Dr Scholl's Wart Remover; Duofilm; Duoplant; Fostex Acne Medication Cleansing; Freezone; Gordofilm; Hydrisalic; Ionil Plus†; Ionil; Keralyt; Mediplast; MG217 Sal-Acid; Mosco; Occlusal; Off-Ezy; Oxy Night Watch; P & S; Panscol; PropapH; Psor-a-set; Psoriasin Medicated Wash; SA; Sal-Acid†; Sal-Plant; Salac†; Salactic Film; Salacyn; Salex; Salkera; Salvax; Stri-Dex Clear; Trans-Ver-Sal AdultPatch; Trans-Ver-Sal PediaPatch; Trans-Ver-Sal PlantarPatch; Virasal; Wart Remover; Wart-Off; X-Seb; *Venez.*: Acnil; Neutrogena T-Sal.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Fr.*: Billerol.

Pharmacopoeial Preparations
BP 2014: Coal Tar and Salicylic Acid Ointment; Compound Benzoic Acid Ointment; Dithranol and Salicylic Acid Ointment; Dithranol Paste; Salicylic Acid Collodion; Salicylic Acid Cream; Salicylic Acid Ointment; Zinc and Salicylic Acid Paste;
BPC 1973: Salicylic Acid and Sulphur Ointment;
USP 36: Benzoic and Salicylic Acids Ointment; Salicylic Acid Collodion; Salicylic Acid Gel; Salicylic Acid Plaster; Salicylic Acid Topical Foam; Zinc Oxide and Salicylic Acid Paste.

Salnacedin *(USAN, rINN)*

G-201; Salnacedina; Salnacédine; Salnacedinum; SCY; Сальнацедин.
N-Acetyl-L-cysteine salicylate.
$C_{12}H_{13}NO_5S$=283.3
CAS — 87573-01-1.
UNII — 02X9QIP2NU.

Profile

Salnacedin has anti-inflammatory and keratolytic properties and is applied topically in the treatment of seborrhoeic dermatitis and acne.

Sebacic Acid

Ácido decanodioico; Sebácico, ácido; Себациновая Кислота.
Decanedioic acid; Octane-1,8-dicarboxylic acid.
$C_{10}H_{18}O_4$=202.2
CAS — 111-20-6.
UNII — 97AN39IKTC.

Profile

Sebacic acid may be used as a buffering agent in cosmetic preparations. Some of its esters, such as diethyl sebacate ($C_{14}H_{26}O_4$ = 258.4) and diisopropyl sebacate ($C_{16}H_{30}O_4$ = 286.4) may be used as emollients.

Selenium Sulfide

Seleenidisulfidi; Selendisulfid; Seleni Disulfidum; Selenii disulfidum; Selenio, sulfuro de; Sélénium, disulfure de;

Selenium Disulphide; Selenium Sulphide; Seleno disulfidas; Sulfid selenitý; Szelén-diszulfid; Сульфид Селения.
SeS_2=143.1
CAS — 7488-56-4.
ATC — D01AE13.
ATC Vet — QD01AE13.
UNII — Z69D9E381Q.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Ph. Eur. 8: (Selenium Disulfide; Selenium Sulfide BP 2014). A bright orange to reddish-brown powder. Practically insoluble in water.

USP 36: (Selenium Sulfide). A bright orange to reddish-brown powder with not more than a faint odour. Practically insoluble in water and in organic solvents; soluble 1 in 161 of chloroform and 1 in 1667 of ether.

Uses and Administration

Selenium sulfide has antifungal and antiseborrhoeic properties. It is used topically in the treatment of dandruff (pityriasis capitis) and seborrhoeic dermatitis of the scalp (p. 1689.1). Five to 10 mL of a lotion or shampoo containing 2.5% of selenium sulfide is applied to the wet scalp; the hair is rinsed and the application repeated; the preparation should remain in contact with the scalp for 2 to 3 minutes each time. The hair should be well rinsed after the treatment and all traces of the preparation removed from the hands and nails. Applications are usually made twice weekly for 2 weeks, then once weekly for 2 weeks and then only when necessary. Shampoos and lotions containing 1% are also used.

Selenium sulfide is also used as a 2.5% lotion in the treatment of pityriasis versicolor (see Skin Infections, p. 568.1). The lotion may be applied to the affected areas with a small amount of water and allowed to remain for 10 minutes before thorough rinsing. This procedure is repeated once daily for about 7 days. Alternatively undiluted 2.5% lotion has been applied at bedtime and washed off in the morning on 3 separate occasions at 3-day intervals.

Selenium sulfide has also been used as an adjunct to the systemic treatment of tinea capitis (see Dermatophytoses under Skin Infections, p. 568.1).

Adverse Effects, Treatment, and Precautions

Topical application of selenium sulfide can produce irritation of the scalp and skin, especially in the genital area and skin folds. Treated areas should be rinsed thoroughly to reduce inflammation, and contact with the eyes should be avoided. Oiliness or dryness of the scalp or hair, hair discoloration, and hair loss have been reported. Selenium sulfide shampoos should not be used within 48 hours of applying hair colours or straightening or waving preparations. Selenium sulfide may discolour metals.

Only traces of selenium sulfide are absorbed through intact skin but prolonged use on broken skin has resulted in systemic toxicity. To minimise absorption it should not be applied to mucous membranes or to skin that is inflamed or damaged. Toxicity is expected to be low from the ingestion of shampoos containing selenium sulfide. Nausea, vomiting, and diarrhoea may occur and gastrointestinal decontamination is generally considered unnecessary, but systemic absorption and toxicity, particularly neurological effects, might develop if large amounts are retained in the gut.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies selenium sulfide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Systemic toxicity. A woman with excoriated eruptions on her scalp developed weakness, anorexia, abdominal pain, vomiting, tremors, sweating, a metallic taste in her mouth, and a garlic-like smell on her breath after using a shampoo containing selenium sulfide 2 or 3 times weekly for 8 months.[1] All symptoms subsided 10 days after the shampoo was stopped.

1. Ransone JW, *et al.* Selenium sulfide intoxication. *N Engl J Med* 1961; **264:** 384–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Selsun; ***Austria***: Selsun; Selukos; ***Belg.***: Selsun; ***Braz.***: Caspacil; Selsun; ***Canad.***: Versel; ***Chile***: Selsun; ***China***: Xi Er Sheng (希尔生); ***Denm.***: Selsun†; ***Fin.***: Selsun†; Selukos; ***Fr.***: Selsun; Vichy Dercos Shampooing Antipelliculaire; ***Ger.***: Selsun; Selukos†; ***Gr.***: Selsun; ***Hong Kong***: Sellon; Selsun†; ***Indon.***: Selsun; Topisel†; ***Irl.***: Selsun; ***Israel***: Sebosel; Selsun; ***Ital.***: Selsun Blu; ***Malaysia***: Sellon; ***Neth.***: Selsun; ***Norw.***: Selsun; Selukos; ***NZ***: Selsun; ***Philipp.***: Selsun Blue†; ***Pol.***: Selsun; ***Port.***: Finitor; Selenix; ***S.Afr.***: Selsun; ***Singapore***: Seldron; Selsun; ***Spain***: Bioselenium; Caspiselenio†; ***Swed.***: Selsun; Selukos; ***Switz.***: Selsun; ***Thai.***: Sebosel; Selfide; Sellon; Selsun; ***Turk.***: Selsun; ***UK***: Selsun; ***USA***: Head & Shoulders Intensive Treatment; Selenos; SelRx; Selsun; ***Venez.***: Selegel.

Multi-ingredient Preparations. ***Arg.***: Selegel; ***Chile***: Selegel; Shampoo Anti Caspa Fortificante; Shampoo Anti-Caspa; ***Fr.***: Selegel†; ***India***: Candid-TV; Dandruff Plus; ***Spain***: Sebumselen; ***Switz.***: Ektoselene; ***Venez.***: Selenil.

Pharmacopoeial Preparations
BP 2014: Selenium Sulphide Scalp Application;
USP 36: Selenium Sulfide Topical Suspension.

Sinecatechins *(USAN)*

Kunecatechins.
A mixture whose major constituents are (-)-epicatechin, (-)-epigallocatechin, the corresponding 3-gallate esters, and their corresponding epimers.
CAS — 811420-59-4 (sinecatechins); 490-46-0 ((-)-epicatechin); 1257-08-5 ((-)-epicatechin 3-O-gallate); 970-74-1 ((-)-epigallocatechin); 989-51-5 ((-)-epigallocatechin 3-O-gallate).
UNII — W2ZU1RY8B0 (green tea leaf); T432289GYZ (sinecatechins).

NOTE. The name Polyphenon E has been used as a trade mark for sinecatechins-containing preparations.

Profile

Sinecatechins is a mixture of complex polyphenols extracted from green tea leaves. Although its mechanism of action is unclear, sinecatechins is used in the treatment of external genital and perianal warts (p. 1689.3). A 15% ointment is applied 3 times daily until complete clearance of all warts, but for no longer than 16 weeks. Local adverse effects are common with the topical application of sinecatechins and include erythema, pruritus, burning, pain or discomfort, erosion or ulceration, oedema, induration, and vesicular rash. Less common effects include urethritis, pigmentation changes, and hyperaesthesia.

References.
1. Gross G, *et al.* A randomized, double-blind, four-arm parallel-group, placebo-controlled phase II/III study to investigate the clinical efficacy of two galenic formulations of Polyphenon E in the treatment of external genital warts. *J Eur Acad Dermatol Venereol* 2007; **21:** 1404–12.
2. Anonymous. Veregen: a botanical for treatment of genital warts. *Med Lett Drugs Ther* 2008; **50:** 15–16.
3. Gross G. Polyphenon E: Eine neue topische Therapie für Condylomata acuminata. *Hautarzt* 2008; **59:** 31–5.
4. Stockfleth E, *et al.* Topical Polyphenon E in the treatment of external genital and perianal warts: a randomized controlled trial. *Br J Dermatol* 2008; **158:** 1329–38.
5. Tatti S, *et al.* Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol* 2008; **111:** 1371–9.
6. Tatti S, *et al.* Polyphenon E: a new treatment for external anogenital warts. *Br J Dermatol* 2010; **162:** 176–184.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Israel***: Veregen; ***Ital.***: Epinerve; ***USA***: Veregen.

Multi-ingredient Preparations. ***Indon.***: Liproqy; Vipro-G; Vipro-G; ***Ital.***: Legalon Plus; ***USA***: Dexatrim Max Daytime Appetite Control.

Skin Substitutes

Sustitutos de la piel.

Profile

Biological and semisynthetic materials have been developed for use as temporary dressings in burns, ulcers, and other injuries associated with skin loss. The rationale is to prevent fluid and heat loss, to reduce infection, to protect exposed structures, to reduce pain, and to prepare the site for grafting (see Burns, p. 1683.1, and Wounds and Ulcers, p. 1690.1).

Denatured porcine and bovine skin, consisting of the dermal and/or epidermal layers, have been used. More recently bioengineered human skin equivalents have been produced which more closely mimic human skin, as well as human, living dermal replacement products.

Reviews.
1. Supp DM, Boyce ST. Engineered skin substitutes: practices and potentials. *Clin Dermatol* 2005; **23:** 403–12.
2. Braye F, *et al.* Les substituts cutanés reconstruits en laboratoire: application au traitement des brûlés. *Pathol Biol (Paris)* 2005; **53:** 613–17.
3. Bar-Meir E, *et al.* Skin substitutes. *Isr Med Assoc J* 2006; **8:** 188–91.
4. Hrabchak C, *et al.* Biological skin substitutes for wound cover and closure. *Expert Rev Med Devices* 2006; **3:** 373–85.
5. Blozik E, Scherer M. Skin replacement therapies for diabetic foot ulcers: systematic review and meta-analysis. *Diabetes Care* 2008; **31:** 693–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Kytinon Hemostatico; Kytinon Kit; Kytinon Lamina; Kytinon Q4; ***S.Afr.***: Dermagraft†; ***UK***: Dermagraft; Myskin; TransCyte; ***USA***: Apligraf; Dermagraft; Orcel; TransCyte.

Multi-ingredient Preparations. ***Arg.***: Kytinon ABC; Kytinon ATM.

Sodium Ascorbyl Phosphate

Ascorbil Fosfato de Sodio; Sodium Ascorbyl Monophosphate; Trisodium Ascorbate-2-phosphate.
$C_6H_6Na_3O_9P$=322.0
CAS — 66170-10-3.
UNII — 836SJG51DR.

Profile

Sodium ascorbyl phosphate is a derivative of vitamin C (p. 2110.3) with antioxidant properties. It is used topically in preparations for skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Indon.***: Probio-C; ***Mex.***: Cetoxic; ***Venez.***: Cepin.

Sodium Pidolate *(pINNM)*

NaPCA; Natrii Pidolas; Pidolate de Sodium; Pidolato sódico; Piroglutamato sódico; Pirrolidona carboxilato de sodio; Sodium Pyroglutamate; Sodium Pyrrolidone Carboxylate; Натрий Пидолат.
Sodium 5-oxopyrrolidine-2-carboxylate.
$C_5H_7NNaO_3$=152.1
CAS — 28874-51-3 (DL-sodium pidolate); 54571-67-4 (L-sodium pidolate).
UNII — 1V74VH163T (L-sodium pidolate); 469OTG57A2 (DL-sodium pidolate).

Profile

Sodium pidolate is used as a humectant. It is applied topically as a cream or lotion, often in multi-ingredient preparations, in the treatment of dry skin disorders.

Copper and zinc pidolate are used similarly; they have also been used as nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Effaclar; Nicozinc; ***Hong Kong***: DermaVeen†.

Multi-ingredient Preparations. ***Arg.***: Lacticare; Nicozinc; ***Austria***: Dermadrate; FootSmart; Papulex; ***Braz.***: Effaclar; Lacticare; ***Chile***: Effaclar Agua Desmaquillante Purificante; Effaclar Hidratante Matificante Activa; Effaclar K; Kerium Anticaspa Cast a Grasa; Normaderm Barra de Limpieza; Uriage Cu-Zn; ***Fr.***: Bi-Zinc†; Cu-Zn; Effaclar K; Forcapil; Hydracuivre; Hysek; Lacticare†; Mycogel†; Papulex; ***Hong Kong***: Dermadrate; D Emulsion†; Mycogel†; ***Hung.***: Forcapil; ***India***: Aloederm-1; Efaderm; Efatop-PE; ***Indon.***: Lacticare†; ***Irl.***: Effaclar K; Effacla; Hydromol; Lacticare†; ***Ital.***: Angstrom Viso; ***Malaysia***: Aqu Care; Lacticare; ***Mex.***: Lacticare; ***NZ***: Dermadrate†; ***Philipp.***: Lacticare; ***S.Afr.***: Lacticare†; ***Singapore***: Dermadrate; Derma vive; Effaclar K; Lacticare; Papulex Isocorrexion; Papulex Oil Free; Stop-Itch Plus; ***Thai.***: Lacticare; ***UK***: Hydromol.

Squaric Acid Dibutylester

Éster dibutílico del ácido escuárico; Quadratic Acid Dibutylester; SADBE; Дибутиловый Эфир Сквариковой Кислоты.
The dibutyl ester of 3,4-dihydroxy-3-cyclobutene-1,2-dione; 3,4-Dibutoxy-3-cyclobutene-1,2-dione.
$C_{12}H_{18}O_4$=226.3
CAS — 2892-62-8 (squaric acid dibutylester); 2892-51-5 (squaric acid).
UNII — 4RTO57VG6S.

Profile

Squaric acid dibutylester has been tried similarly to diphencyprone (p. 1700.3) as a contact sensitiser in the treatment of alopecia. It has also been tried in warts.

References.
1. Tosti A, *et al.* Long-term results of topical immunotherapy in children with alopecia totalis or alopecia universalis. *J Am Acad Dermatol* 1996; **35:** 199–201.

2. Micali G, *et al.* Treatment of alopecia areata with squaric acid dibutylester. *Int J Dermatol* 1996; 35: 52–6.
3. Lee AN, Mallory SB. Contact immunotherapy with squaric acid dibutylester for the treatment of recalcitrant warts. *J Am Acad Dermatol* 1999; 41: 595–9.
4. Silverberg NB, *et al.* Squaric acid immunotherapy for warts in children. *J Am Acad Dermatol* 2000; 42: 803–8.
5. Micali G, *et al.* Use of squaric acid dibutylester (SADBE) for cutaneous warts in children. *Pediatr Dermatol* 2000; 17: 315–18.
6. Dall'Oglio F, *et al.* Adult and paediatric contact immunotherapy with squaric acid dibutylester (SADBE) for recurrent, multiple, resistant, mucocutaneous anogenital warts. *Sex Transm Infect* 2002; 78: 309–10.
7. Dall'Oglio F, *et al.* Topical immunomodulator therapy with squaric acid dibutylester (SADBE) is effective treatment for severe alopecia areata (AA): results of an open-label, paired-comparison, clinical trial. *J Dermatol Treat* 2005; 16: 10–14.
8. Ajith C, *et al.* Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in alopecia areata and factors influencing the outcome. *J Drugs Dermatol* 2006; 5: 262–6.
9. Hama N, *et al.* Usefulness of topical immunotherapy with squaric acid dibutylester for refractory common warts on the face and neck. *J Dermatol* 2009; 36: 660–2.

Sulfur

Azufre; Enxófre; Kén; Kükürt; Rikki; Schwefel; Siarka; Síra; Soufre; Sulphur; Sulphurium; Svavel; Cepa.

S=32.06

CAS — 7704-34-9.
ATC — D10AB02.
ATC Vet — QD10AB02.
UNII — 70FD1KFU70.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. Some have monographs for Precipitated Sulfur (Milk of Sulfur), Sublimed Sulfur (Flowers of Sulfur), or both. Some specify it is only for external use.

Eur. also includes for homoeopathic preparations.

Ph. Eur. 8: (Sulfur for External Use). A yellow powder. The size of most of the particles is not greater than 20 micrometres and that of almost all the particles is not greater than 40 micrometres. Practically insoluble in water; soluble in carbon disulfide; slightly soluble in vegetable oils. Protect from light.

Ph. Eur. 8: (Sulfur for Homoeopathic Preparations; Sulfur ad Praeparationes Homoeopathicas). A yellow powder. Practically insoluble in water; soluble in carbon disulfide; slightly soluble in vegetable oils. Protect from light.

USP 36: (Precipitated Sulfur). A very fine, pale yellow, odourless, amorphous or microcrystalline powder. Practically insoluble in water; very slightly soluble in alcohol; slowly and usually incompletely soluble 1 in 2 of carbon disulfide; soluble 1 in 100 of olive oil.

USP 36: (Sublimed Sulfur). A fine, yellow, crystalline powder with a faint odour. Practically insoluble in water and in alcohol; sparingly soluble in olive oil.

Uses and Administration

Sulfur is a keratolytic, a mild antiseptic, a mild antifungal, and a parasiticide.

Colloidal sulfur has a smaller particle size than either precipitated or sublimed sulfur. It is sulfur in an aqueous medium containing a colloid such as albumin or gelatin.

Sulfur has been widely used in lotions, creams, or ointments, usually combined with other agents, in concentrations of up to 10% in the treatment of acne, dandruff, seborrhoeic conditions, scabies, and superficial fungal infections, although there are more convenient and effective preparations.

Lotions of precipitated sulfur with lead acetate have been used to darken grey hair.

Sulfur was also formerly used as a mild irritant laxative.

Homoeopathy

Sulfur has been used in homoeopathic medicines under the following names: Sulphur.

General references.
1. Lin AN, *et al.* Sulfur revisited. *J Am Acad Dermatol* 1988; 18: 553–8.
2. Gupta AK, Nicol K. The use of sulfur in dermatology. *J Drugs Dermatol* 2004; 3: 427–31.

Adverse Effects and Precautions

Topical application of sulfur can cause skin irritation and dermatitis has been reported after repeated application. Contact with the eyes, mouth, and other mucous membranes should be avoided. Contact with sulfur can discolour certain metals such as silver, and application of sulfur with topical mercurial compounds can lead to the generation of hydrogen sulfide which has a foul odour and may stain the skin black.

Handling. Sulfur has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies sulfur as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Macbirs Sulphur; Molnia; *Canad.*: Aloepure; Rodan & Fields Proactiv Refining Mask†; *India*: Dermosol; *Indon.*: Acne Feldin; JF Sulfur†; *Ital.*: Acqua Sirmione; Eudermal Sapone Allo Zolfo pH 5; Misurid; *Malaysia*: JF Sulfur; *Neth.*: Schwef-Heel; *Philipp.*: Brasul; Suldermt; *Port.*: Acnederma†; *Turk.*: Capila Savon; *USA*: Acne Lotion 10; Liquimat; Sulfoam; Sulmasque.

Multi-ingredient Preparations. *Arg.*: Azufracid; Bentophyto; Bifena; Parmigras; Medicatex; Merbenloc; Nemegel; Novofarma; Novofarma; Onelacne; Pinklot; Sastid; Suffisance; Ukase Dermo; Xicanil Control†; *Austral.*: Clearasil Pimple Treatment Cream†; EgoPsoryl TA; Eskamel†; Neo-Medrol†; Psor-Asist; Psor-Asist; *Austria*: Aknichthol; Eucarbon; Herposicc; Schwefelbad Dr Klopfer; *Braz.*: Acnase; Actine; Dermax; Dermict; Dermolimp; Salder S; Salisoap; Salisoap; Sastid; *Canad.*: Acnomel†; Clearasil Acne Control†; Clearasil Acne Cream†; Clearasil Stayclear†; Mazon Medicated Shampoo; Medrol Acne Lotion; Meted†; Neo-Medrol Acne; Sebo Concept D/A; Sebulex†; Sterex Plus†; Sterex†; Sulfacet-R; *Chile*: Dermac Crema; Sastid Jabon; *Cz.*: Eucarbon; *Fr.*: Dermo-Sulfuryl; Kertyol PSO; Kertyol PSO; Notrinot; Paps†; Selso; Solacy; Sulfuryl; Zeniac; *Ger.*: Schwefelbad Dr Klopfer†; *Gr.*: Creme Phyllis de Jeunesse; Medrol Acne Lotion; Neo Akmine; Neo-Medrol; Rysolone; *Hong Kong*: Acne-Aid†; BF-2-4-2†; Egopsoryl TA; Neo-Medrol Acne; Sastid; *Hung.*: Bolus Laxans; Eucarbon; Schwefelbad Dr Klopfer†; *India*: Acnil; Coalsyl-S; Persol Forte; *Indon.*: Bioacne; Feldixid†; Salicyl-Zwavelzalf; Sastid†; *Irl.*: Cocois; Meted; Pragmatar†; Skin Clear†; *Israel*: Duo-Scabil; Eucarbon; Neo-Medrol; *Ital.*: Acnesan; Anti-Acne; Eucarbon; Geroderm Zolfo; Lenirose; Sacnel; Same-Seb; Saugella Solido Zolfo; Troca Flu Spray Nasale; *Jpn*: Circanetten; *Malaysia*: Acne-Aid†; Clearasil Pimple Treatment; Egopsoryl TA; Eucarbon; Neo-Medrol; Nixoderm; Panoff; Sastid; *Mex.*: Acnomel; Axel; Axel; Dermac Jabon del Tio Nacho; Sastid; *NZ*: Clearasil; Coco-Scalp; Egopsoryl TA; *Philipp.*: Dermalin†; Sastid; *Pol.*: Acne Sulf†; Bals-Sulphur; Cocois; Dermaknel†; Zdroj; *Port.*: Resodermil†; *Rus.*: Sulfodecortem (Сульфодекортэм); *S.Afr.*: Balsem Sulphuris; Clearasil T†; Eskamel†; Haarlemensis; Neo-Medrol†; Sastid; Zeel; Zeel; *Singapore*: Acne Clear; Acne-Aid†; Clearasil Pimple Treatment; Cocois Co; Cocois; Egopsoryl TA; Neo-Medrol; Nixoderm; Panoff; Poly-N; Sastid; Veelanz's Ointment; *Spain*: Crislaxo; Laxante Sanatorium†; *Swed.*: Sevorex; *Switz.*: Acne Creme; Acne Gel; Ektoselene; Sebo-Soufrol†; *Thai.*: Circanetten; Neo-Medrol; Sastid†; *Turk.*: Eucarbon; Karboseptin; Wilkinson†; *UK*: Actinac†; Balto Foot Balm; Clearasil Active Treatment Cream; Cocois; Herbheal Ointment; Meted; Psorasolv; Sebco; Simpsons; Skin Clear; TCP; *Ukr.*: Eucarbon (Эукарбон); *USA*: Acno; Acnomel; Acnotex; Ala seb T; ala seb; Avar; Aveeno Cleansing Bar†; Bensulfoid; Boil Ease; BP Cleansing Wash; Cerisa; Chigg Away; Claris; Cleniat; Exoderm; Finac; Fostex Medicated; Garimide; Meted; MG217 Medicated Tar-Free; MG400; Nicosyn; NuOx; Pazol XS; Pernox; Plexion; Rezamid; Rosact; Rosaderm; Rosanil; Rosula†; Sastid; SE SS; Seale's Lotion; Sebasorb; Sebex-T; Sebex; Sebulex; SSS; Sulfacet-R; SulfaCleanse; Sulforcin; Sulfoxyl; Sulpho-Lac; SulZee†; Sumadan; Sumaxin; Suphera; Virti-Sulf; Zencia; Zetacet†; *Venez.*: Klenyl; Klenyl; Niosilin; Selenil.

Homoeopathic Preparations. *Austral.*: Echine†; Homoderma; *Austria*: Acidum picrinicum Med Complex†; Engystol; Erbiode Akne; Erysidoron Nr 2; Mandragora Med Complex; Ohrentropfen Similasan; Sulfur Med Complex; *Canad.*: Adrisin†; Art Complex†; Arthflex; Backache with Arnica†; Berberis-Homaccord†; Calendula +; Calms Forte 4 Kids; Calsom†; Cutisitum†; Earache; Echinacea Compositum; Echinacea L40†; Eczema L87; Endoteel†; Engystol; Erysidoron 2†; Euphorbium Compositum; Euphorbium Compositum; Execaim†; Formula DE 226†; Formula PC 223†; Hae 1 Complex†; Hepar Compositum; Homeo-Form G†; Hyalgesic LBP†; Ikoplex 12†; Indigestion†; Luffeel Nasal Spray; SK Complex†; Sorinoheel; Ubicoenzyme; Urarthone†; Zeel Comp; *Chile*: Grippakit; Ikoplex No 12; *Cz.*: Engystol; Luffeel; Paragrippe; Zeel Compositum; Zeel Salbet†; *Fr.*: Abbe Chaupitre no 19†; Abbe Chaupitre no 1†; Abbe Chaupitre no 22†; Abbe Chaupitre no 35†; Abbe Chaupitre no 79†; Abbe Chaupitre no 82†; Abbe Chaupitre no 83†; Abbe Chaupitre no 88†; Abbe Chaupitre no 91†; Aesculus Complexe No 103; Basilicum Complexe No 96; Cholesterolum Complexe No 112†; Echinacea Complexe No 40; Euphorbium Complexe No 88; Geranium Complexe No 108†; grippet†; Hypophysis Complexe No 31†; Jenoverine†; Millefolium Complexe No 7†; Nux Vomica Complexe No 49; Paragrippe; Pulsatilla Complexe No 60†; Rhododendron Complexe No 42†; Scabiosa Complexe No 87; Sclerocalcine; Staphysagria Complexe No 92†; Sulfur Complexe No 12; Symphytum Complexe No 48†; Urarthone; *Ger.*: Asthmakhell N; BN dolo†; Cefalymphat†; Cefasulfon N†; Chamoca M; Colchicum Complex; Colintest-Gastreu; Cysto-cyl L Ho-Len-Complex; Derma-Plantin†; Dermi-cyl L Ho-Len-Complex; Engystol; Erysidoron 2; Gastro-Plantin N†; Genu-cyl L Ho-Len-Complex; Haemorrhoid-Gastreu N; Hepar comp; Hewerheum N†; Hexacyl; Luffeel Comp; Lymphaden Complex; Lymphaden; metabiarex; Mucosa compositum; Regenaplex Haut G; Rufebran rheumo†; Sulfurell; Toxiselect; Zeel comp; *Hung.*: Klimakt-Heel; Luffeel; Zeel; *Neth.*: Aesculus Comp; Asakeil; Asthmakhell†; Auriculite; Bronchilite; Dermafleur; Dermalite; Echinacea comp; Engystol; Hemorrolite; Homeocare Revito; Jenoverine†; Luffeel E; Lymfelite; Paragrippe†; Prurilite; Pulsatilla comp; Thuyalite; Urtizon complex; Zeel comp N; *Port.*: Paragrippe; *Rus.*: Tabacum-Plus (Табакум-Плюс); Urtica-Plus (Уртика-Плюс); Zeel T (Цель Т); *S.Afr.*: Engystol N; Erysidoron 2†; *Switz.*: Engystol; Regenaplex Nr. 25a; Regenaplex Nr. 31b; Regenaplex Nr. 49a; Regenaplex Nr. 71b; *UK*: Erysidoron 2; *Ukr.*: Engystol (Энгистол); *USA*: Eczemol.

Pharmacopoeial Preparations

BPC 1973: Salicylic Acid and Sulphur Ointment;
USP 36: Resorcinol and Sulfur Topical Suspension; Sulfur Ointment.

Sulfurated Lime

Cal sulfurada; Calcium Sulphide; Calx Sulphurata; Sulfuro cálcico; Sulphurated Lime; Сульфид Кальция (calcium sulfide); Сернистый Кальций (calcium sulfide).

CAS — 8028-82-8 (sulfurated lime solution); 20548-54-3 (calcium sulfide); 1344-81-6 (calcium polysulfide).

Profile

Sulfurated lime is a mixture containing calcium sulfide (CaS) and not more than 50% of calcium sulfate (p. 2173.1); it is prepared by heating calcium sulfate with carbonaceous matter. Sulfurated lime solution (Vleminckx's solution) is an aqueous solution containing calcium polysulfides and calcium thiosulfate prepared by boiling sublimed sulfur with calcium hydroxide in water.

Sulfurated lime has been used topically as sulfurated lime solution for acne, scabies, seborrhoeic dermatitis, and pustular infections such as boils and carbuncles. A similar solution known as 'lime-sulphur' (lime sulfur) is used as a fungicide in horticulture.

Homoeopathy

An impure grade of calcium sulfide has been used in homoeopathic medicines under the following names: Hepar sulfuris; Hepar sulfuris calcareum; Hepar Sulphuris; Hepar Sulph.; Hepar sulphuris calcareum; Hepar sulph calc.

NOTE. The name Hepar Sulfuris is also applied to Sulfurated Potash (see below).

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Austral.*: Childrens Cough Relief; Childrens Runny Nose Relief; Earache Relief†; Respatona Chesty Cough & Nasal Congestion; Respatona Head Cold; Respatona Nasal Spray Decongestant; Respatona Sinus Relief; *Austria*: Echinacea-Cosmoplex; Euphorbium Compositum; Globuli gegen Kopfschmerzen; Globuli gegen Schlafstorungen; Nebenhohlen-Tropfen Nr 26†; Rhododendroneel; Tonsiotren; Traumeel; *Canad.*: Angeel†; Calnor†; ClearAc†; Crou Complex†; Echinacea Compositum; Euphorbium Compositum; *Euphorbium Compositum*; Homeo-Form SI†; Homeovox; Hylands Cough; Hylands Formula CA; Larydol†; Nareel†; Rhinar†; Sinus Ease; Sinus; Sinuspax†; Traumeel; *Cz.*: Angin-Heel S; Euphorbium Compositum; Homeovox; Traumeel; *Fr.*: Abbe Chaupitre Hivernum No 5†; Abbe Chaupitre no 1†; Abbe Chaupitre no 48†; Abbe Chaupitre no 91†; Boripharm No 10†; Boripharm No 22†; Homeovox; Sinuspax; Voxpax; *Ger.*: Dermi-cyl L Ho-Len-Complex; Entzundungstropfen; Euphorbium comp SN; Gastritis Complex; Haut-Gastreu R60; Hevertotox; Immunorell; Infihepan; Odonton-Echtroplex; Otofren; Roth's RKT Tropfen; Rufebran bronchot; Schworosin; Sinusitis Hevert SL; Sinusitis Hevert†; Tonsiotren H; toxi-loges; Traumeel S; *Hung.*: Homeovox; Traumeel; *Neth.*: Emvita 10; Emvita 3; Habifac Hemorrolite; Homeovox; Kind 0-3 Chamodent; Lergilite; Mercurius-Heel; Prurilite; Sabal-Homaccord; Thuyalite; Tonsiotreen; Traumeel S; *Port.*: Homeovox; *Rus.*: Homeovox (Гомеовокс); Sabal-Homaccord (Сабаль-Гомаккорд); Tonsilotren (Тонзилотрен); *S.Afr.*: Euphorbium Compositum S†; Traumeel S; *Switz.*: Homeovox; Regenaplex Nr. 50b; Sinuspax†; Traumeel; TussEx; *Ukr.*: Dentokind (Дентокинд); Homeovox (Гомеовокс); Tonsilotren (Тонзилотрен); Traumeel S (Траумель С); *USA*: Traumeel; *Venez.*: Traumeel.

Sulfurated Potash

Foie de Soufre; Hepar Sulfuris; Hígado de azufre; Kalii Sulfidum; Liver of Sulphur; Potasa sulfurada; Potassa Sulphurata; Schwefelleber; Sulphurated Potash; Сернаа Печень.

CAS — 39365-88-3.

NOTE. The title Hepar Sulphuris is used in homoeopathic medicine for an impure grade of calcium sulfide—see Sulfurated Lime, above.

Pharmacopoeias. In *US*.

USP 36: (Sulfurated Potash). A mixture composed chiefly of potassium polysulfides and potassium thiosulfate, containing not less than 12.8% of sulfur as sulfide. Irregular, liver-brown pieces when freshly made, changing to greenish-yellow. It has an odour of hydrogen sulfide. Soluble 1 in 2 of water, usually leaving a slight residue. Alcohol dissolves

only the sulfides. A 10% solution is light brown in colour and alkaline to litmus. Store in small, airtight containers.

Incompatibility. Sulfurated potash is incompatible with acids.

Profile

Sulfurated potash has been used in the treatment of acne and other skin disorders usually in the form of a lotion with zinc sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Cz.*: Lamioflur†; *Ger.*: Sinasal; *Hung.*: Angin-Heel; *Rus.*: Belladonna-Plus (Белладонна-Плюс); Pharyngomed (Фарингомед); Phytolacca-Plus (Фитолакка-Плюс); Rhus-Plus (Рус-Плюс); Traumeel S (Траумель С).

Pharmacopoeial Preparations
USP 36: Zinc Sulfide Topical Suspension.

Sulisobenzone *(USAN, rINN)*

Benzofenon-4; Benzophenone-4; NSC-60584; Sulisobenzona; Sulisobenzonum; Сулизобензон.
5-Benzoyl-4-hydroxy-2-methoxybenzenesulphonic acid.
$C_{14}H_{12}O_6S$=308.3
CAS — 4065-45-6.
UNII — 1W6L629B4K.

NOTE. Escalol 577 and Uvinul MS 40 are trade names that have been used for sulisobenzone.

Pharmacopoeias. In *US.*

USP 36: (Sulisobenzone). Light tan powder. M.p. about 145 degrees. Freely soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in ethyl acetate. Store in airtight containers. Protect from light.

Profile

Sulisobenzone, a substituted benzophenone, is a sunscreen (p. 1681.3) with actions similar to those of oxybenzone (p. 1715.3). It is effective against UVB and some UVA light (for definitions, see p. 1685.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Nubevital BB; Nubevital Sunblock Ultra; Refrane Plus; *Braz.*: Sunmax Acqua; *Chile*: Hidrafil†; Spectraban 55; *Mex.*: Hidrafil; Spectraban 55; *USA*: Hawaiian Tropic Protective Tanning Dry.

T4 Endonuclease V

Bacteriophage T4 Endodeoxyribonuclease V; T4 Эндонуклеаза V; T4N5.
Coliphage T4 endodeoxyribonuclease V.
CAS — 52227-85-7.

NOTE. The name Dimericine has been used as a trade mark for T4 endonuclease V.

Profile

T4 endonuclease V is a DNA-repair enzyme that is reported to remove DNA damaged by UV radiation. It is under investigation to reduce the incidence of actinic keratosis and basal cell carcinoma in patients with xeroderma pigmentosum (see Photosensitivity Disorders, p. 1686.2).

References.

1. Wolf P, *et al.* Topical treatment with liposomes containing T4 endonuclease V protects human skin in vivo from ultraviolet-induced upregulation of interleukin-10 and tumor necrosis factor-α. *J Invest Dermatol* 2000; 114: 149–56.
2. Yarosh D, *et al.* Effect of topically applied T4 endonuclease V in liposomes on skin cancer in xeroderma pigmentosum: a randomised study. *Lancet* 2001; 357: 926–9.
3. Cafardi JA, Elmets CA. T4 endonuclease V: review and application to dermatology. *Expert Opin Biol Ther* 2008; 8: 829–38.

Tacalcitol *(BAN, rINN)*

1α,24-Dihydroxycholecalciferol; 1α,24-Dihydroxyvitamin D_3; Tacalcitolum; Takalsitol; Такальцитол.
(+)-(5*Z*,7*E*,24*R*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,24-triol monohydrate.
$C_{27}H_{44}O_3.H_2O$=434.7
CAS — 57333-96-7 (anhydrous tacalcitol); 93129-94-3 (tacalcitol monohydrate).
ATC — D05AX04.
ATC Vet — QD05AX04.
UNII — C2W72OJ5ZU.

Uses and Administration

Tacalcitol is a vitamin D_3 derivative, with actions and uses similar to those of calcipotriol (p. 1697.3).

Tacalcitol is applied topically in the management of plaque psoriasis (p. 1688.1). It is used as the monohydrate, as either a lotion or an ointment, in a concentration equivalent to 4 micrograms/g (0.0004%) of anhydrous tacalcitol. Applications are made sparingly, once daily, preferably at bedtime. No more than 10 mL of lotion or 10 g of ointment should be applied each day. When used together, the total weekly dose of anhydrous tacalcitol should not exceed 280 micrograms (e.g. 30 mL of lotion plus 40 g of ointment). Duration of treatment depends on the severity of the lesions; continuous and intermittent treatments for up to 8 weeks have been used with the lotion, and up to 18 months with the ointment.

Tacalcitol may be degraded by UV radiation and therefore if combined with UV therapy, the radiation should be given in the morning and tacalcitol applied at bedtime.

References.

1. Peters DC, Balfour JA. Tacalcitol. *Drugs* 1997; 54: 265–71.
2. Gollnick H, Menke T. Current experience with tacalcitol ointment in the treatment of psoriasis. *Curr Med Res Opin* 1998; 14: 213–18.
3. Harrison PV. Topical tacalcitol treatment for psoriasis. *Hosp Med* 2000; 61: 402–5.
4. Van de Kerkhof PCM, *et al.* Long-term efficacy and safety of tacalcitol ointment in patients with chronic plaque psoriasis. *Br J Dermatol* 2002; 146: 414–22.
5. Lecha M, *et al.* Tacalcitol in the treatment of psoriasis vulgaris: the Spanish experience. *J Eur Acad Dermatol Venereol* 2005; 19: 414–17.

Adverse Effects and Precautions

As for Calcipotriol, p. 1698.2. Paraesthesia may also occur. Tacalcitol may be applied to the face, but care should be taken to avoid the eyes. Tacalcitol may be degraded by UV radiation (see Uses and Administration, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Curatoderm; *Belg.*: Curatoderm; *Chile*: Bonalfa†; *China*: Bonalfa (萌尔夫); *Cz.*: Curatoderm; *Fr.*: Apsor; *Ger.*: Curatoderm; *Hung.*: Curatoderm; *Israel*: Curatoderm; *Ital.*: Ticlapsor; Vellutan; *Jpn*: Bonalfa; *Mex.*: Bonalfa†; *Pol.*: Curatoderm; *Port.*: Bonalfa; *Spain*: Bonalfa; *Switz.*: Curatoderm; *UK*: Curatoderm.

Purified Talc

E553(b); Mastek; Powdered Talc; Purified French Chalk; Talc; Talco (esteatita); Talco purificado; Talcum; Talcum Purificatum; Talk; Talkas; Talkki; Talkum; Очищенный Тальк.
CAS — 14807-96-6.
UNII — 7SEV7J4R1U.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Talc; Purified Talc BP 2014). A powdered, selected, natural, hydrated, magnesium silicate. Pure talc has the formula $Mg_3Si_4O_{10}(OH)_2$; it may contain varying amounts of associated minerals. A light, homogeneous, white or almost white powder, greasy to the touch (non-abrasive). It should be free from asbestos. Practically insoluble in water, in alcohol, and in dilute solutions of acids and of alkali hydroxides.

USP 36: (Talc). A powdered, selected, natural, hydrated magnesium silicate. It may contain variable amounts of associated minerals among which chlorites (hydrated aluminium and magnesium silicates), magnesite (magnesium carbonate), calcite (calcium carbonate), and dolomite (calcium and magnesium carbonate) are predominant. A very fine, white or greyish-white, unctuous crystalline powder, which adheres readily to the skin, and is free from grittiness.

Uses and Administration

Purified talc is used in massage and as a dusting powder to allay irritation and prevent chafing. It is usually mixed with starch, to increase absorption of moisture, and zinc oxide. Talc used in dusting powders should be sterilised. Purified talc is used as a lubricant and diluent in making tablets and capsules and to clarify liquids.

Sterile purified talc is also used as a sclerosant after drainage of malignant pleural effusion and for recurrent spontaneous pneumothorax. It is administered into the pleural cavity as a slurry or by aerosol (insufflation). Doses of about 5 g may be used for pleural effusion and 2 g for pneumothorax.

Pleural effusions. Talc is used as a sclerosant to achieve pleurodesis in the management of benign and malignant pleural effusions (p. 700.1) and recurrent spontaneous pneumothorax.[1-4] It is generally given into the pleural space as a slurry via intercostal tube, or by insufflation (talc poudrage) at thoracoscopy. Most reports have used a dose of 2 to 5 g, but doses have ranged from 1 to 10 g. A study[5] of talc pleurodesis in patients with malignant pleural effusion found both slurry and insufflation to be equally effective. The most common adverse effects associated with this use of talc are pain and fever. Other reported effects have included local infection and empyema, cardiovascular complications, and respiratory failure (see also Effects on the Lungs, p. 1723.1).

1. Kennedy L, Sahn SA. Talc pleurodesis for the treatment of pneumothorax and pleural effusion. *Chest* 1994; 106: 1215–22.
2. de Campos JRM, *et al.* Thoracoscopy talc poudrage: a 15 year experience. *Chest* 2001; 119: 801–6.
3. Antunes G, *et al.* British Thoracic Society. BTS guidelines for the management of malignant pleural effusions. *Thorax* 2003; 58 (suppl 2): ii29–ii38. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseMalignantPE.pdf (accessed 28/07/08)
4. Henry M, *et al.* British Thoracic Society. BTS guidelines for the management of spontaneous pneumothorax. *Thorax* 2003; 58 (suppl 2): ii39–ii52. Also available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Pleural%20Disease/Guidelines/PleuralDiseaseSpontaneous.pdf (accessed 28/07/08)
5. Dresler CM, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; 127: 909–15.

Adverse Effects and Precautions

Contamination of wounds or body cavities with talc is liable to cause granulomas and it should not be used for dusting surgical gloves.

Inhalation of talc can cause respiratory irritation prolonged exposure may produce pneumoconiosis.

The most common adverse effects of talc pleurodesis are chest pain and fever. More serious complications that can occur include empyema, pneumonitis, dyspnoea, hypoxaemia, pulmonary oedema, pulmonary embolism, acute respiratory distress syndrome, and respiratory failure. Cardiovascular complications such as tachycardia, myocardial infarction, hypotension, hypovolaemia, and asystolic arrest have also occurred in patients treated with talc pleurodesis. However, the role of talc in serious complications is not always clear as the underlying condition of patients with malignant pleural effusion and the procedure itself are likely to be contributing factors.

Talc is liable to be heavily contaminated with bacteria, including *Clostridium tetani*, *Cl. welchii*, and *Bacillus anthracis*. When used in dusting powders or to treat pneumothorax and pleural effusions, it should be sterilised.

Abuse. Adverse pulmonary and ocular effects have been associated with the presence of talc in abused substances. It may be present as an excipient in oral medications that are crushed then dissolved and injected, or it may have been purposely added as a filler to the abused substance. When injected intravenously, the insoluble talc particles can embolise in small pulmonary vessels causing occlusion and pulmonary hypertension. The particles may also then migrate into the pulmonary interstitium, inducing a foreign-body reaction and fibrosis. Irregular nodules can develop in the lungs, which may coalesce to form conglomerate masses.[1] Talc retinopathy is described as deposits of crystalline talc embolising in the retinal microvasculature after intravenous injection.[2-4] Pulmonary granulomas[5] and talc retinopathy[6] have also been described after nasal inhalation of abused substances containing talc.

1. Gotway MB, *et al.* Thoracic complications of illicit drug use: an organ system approach. *Radiographics* 2002; 22 (suppl): S119–S135.
2. Martidis A, *et al.* Talc embolism: a static retinopathy. *Am J Ophthalmol* 1997; 124: 841–3.
3. Fraser-Bell S, Capon M. Talc retinopathy. *Clin Experiment Ophthalmol* 2002; 30: 432–3.
4. El-Jabali F, Cohen S. Talc retinopathy. *N Engl J Med* 2006; 354: e11. Available at: http://content.nejm.org/cgi/reprint/354/12/e11.pdf (accessed 27/09/07)
5. Johnson DC, *et al.* Foreign body pulmonary granulomas in an abuser of nasally inhaled drugs. *Pediatrics* 1991; 88: 159–61.
6. Kumar RL, *et al.* Crystalline retinopathy from nasal ingestion of methamphetamine. *Retina* 2006; 26: 823–4.

Carcinogenicity. A review by a working group of the International Agency for Research on Cancer concluded that there was inadequate evidence to confirm whether purified talc was carcinogenic in humans but there was sufficient evidence to confirm that talc containing asbestiform fibres was carcinogenic to man.[1] There have been suggestions of a link between the use of talc and ovarian cancer[2] but although a case-controlled study suggested an approximate doubling of the risk among women after perineal use of talc the working group noted that information was not available on the asbestos content of the talcs.[1] Further case-controlled studies have also reported a positive association between perineal talc use and ovarian cancer, although others have found no association. A large prospective cohort study[3] that included 78 630 women found little support for an association overall, although from an analysis by histological subtype there appeared to be a modest increase in the risk for serous

invasive cancer. A meta-analysis[4] that included this cohort study and 15 case-controlled studies did find a positive association between any exposure to perineal talc and the risk of developing ovarian cancer (relative risk 1.33; 95% confidence interval 1.16 to 1.45). However, the authors highlighted possible selection bias and confounding factors that may have resulted in a false-positive association. There was a lack of a clear dose-response relationship, different results for hospital-based and population-based patients, and the timing of exposure to talc in relation to cancer diagnosis was not always known.

An analysis of epidemiological studies in workers involved in milling the raw mineral (not containing asbestos-like fibres) found no evidence of an increased risk of lung cancer; there was some evidence of an excess among miners or other industrial workers exposed to talc, but these populations were also exposed to other potential carcinogens.[5]

1. IARC/WHO. Silica and some silicates. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 42* 1987. Available at: http://monographs.iarc.fr/ENG/Monographs/vol42/volume42.pdf (accessed 27/09/07)
2. Longo DL, Young RC. Cosmetic talc and ovarian cancer. *Lancet* 1979; ii: 349–51.
3. Gertig DM, *et al.* Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000; 92: 249–52.
4. Huncharek M, *et al.* Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res* 2003; 23: 1955–60.
5. Wild P. Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. *Occup Environ Med* 2006; 63: 4–9.

Effects on the lungs. Acute respiratory failure has occurred in patients treated with talc pleurodesis, given either as a slurry or by insufflation. In a series of 338 patients treated with insufflation, 4 developed acute respiratory failure and 3 of them died.[1] In another series[2] of 78 patients who underwent 89 procedures using slurry or insufflation, respiratory complications developed after 24 procedures including acute respiratory distress syndrome after 8 procedures in 7 patients of whom 1 died. In a debate based on these and other reports, including some series in which there were no respiratory complications, it was argued[3] that although the risk of acute respiratory distress is small the use of talc for pleurodesis should be abandoned in favour of other drugs such as tetracyclines or bleomycin, or mechanical abrasion of the pleura. The opposing view[4] was that there were many possible causes for acute respiratory distress in these cases, and that talc was still the best pleurodesis agent available. In a prospective randomised comparison in patients with malignant pleural effusion,[5] respiratory complications were more common with insufflation than slurry. The authors noted that the role of talc in causing acute respiratory complications of pleurodesis is unclear and further study is needed.

It has been suggested that acute respiratory distress syndrome after talc pleurodesis may be related to the talc particle size. There were no such reactions in a study[6] of 558 patients given large-particle (mean size 24.5 micrometres) talc insufflation, and the authors suggested that reported cases appeared to occur in countries where talc products contained higher concentrations of small particles (less than 5 micrometres).

For other effects on the lungs, see under Abuse, p. 1722.3 and Infant Skin Care, below.

1. Campos JRM, *et al.* Respiratory failure due to insufflated talc. *Lancet* 1997; 349: 251–2.
2. Rehse DH, *et al.* Respiratory failure following talc pleurodesis. *Am J Surg* 1999; 177: 437–40.
3. Light RW. Talc should not be used for pleurodesis. *Am J Respir Crit Care Med* 2000; 162: 2024–6.
4. Sahn SA. Talc should be used for pleurodesis. *Am J Respir Crit Care Med* 2000; 162: 2023–4.
5. Dresler CM, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. *Chest* 2005; 127: 909–15.
6. Janssen JP, *et al.* Safety of pleurodesis with talc poudrage in malignant pleural effusion: a prospective cohort study. *Lancet* 2007; 369: 1535–9.

Infant skin care. The routine use of non-medicated powders in the skin care of infants can be hazardous and their use should be discouraged.[1,2] Talc acts as a pulmonary irritant and inhalation of baby-powders by infants has caused severe respiratory difficulties and several deaths have been reported. Careful respiratory monitoring is indicated in children suspected of inhaling talcum powder as the onset of symptoms may be delayed for several hours.[1] There have also been reports of umbilical granulomas resulting from contamination of umbilical stumps with talcum powder used for skin care.[2]

1. Pairaudeau PW, *et al.* Inhalation of baby powder: an unappreciated hazard. *BMJ* 1991; 302: 1200–1.
2. Sparrow SA, Hallam LA. Talc granulomas. *BMJ* 1991; 303: 58.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA:* Sclerosol.

Multi-ingredient Preparations. *Arg.:* Dr Selby; Talquisedan; *Austral.:* ZSC; *Austria:* Cutimix; Herposicc; Prurimix; Rombay; *Belg.:* Aloplastine†; *Braz.:* Pomaderme; *Chile:* Talquisedan; *Fr.:* Aloplastine; Poudre du Marcheur†; Supro; *India:* Derby Cool; *Indon.:* Minos†; Yanthi Baby & Bath Powder†; *Israel:* Pedisol†; *Jpn:* Bofutsushosan; Choreito; Choreitogoshimotsuto; Gorinsan; *Malaysia:* Rowarolan; *Mex.:* Hipoglos; *NZ:* Grans Remedy; Lamisil Odor Eze†; *Philipp.:* Johnson's Baby Double Protection Powder; *Pol.:* Pedipur; *Port.:* Cuidaderma; *Rus.:* Teimurov (Теймуров); *Spain:* Amniolina; Ictiomen; *Switz.:* Tanno-Hermal; *Turk.:* Cinkos; *USA:* Caldesene; Columbia Antiseptic Powder.

Pharmacopoeial Preparations
BP 2014: Talc Dusting Powder;
USP 36: Nystatin Topical Powder.

Tars and Tar Oils

Breas y aceites de brea.

Birch Tar Oil

Aceite de abedul; Aceite de brea de abedul; Birkenteer; Goudron de Bouleau; Oleum Betulae Albae; Oleum Betulae Empyreumaticum; Oleum Betulae Pyroligneum; Oleum Rusci; Pix Betulae; Pyroleum Betulae; Масло Березтового Дёгтя.

Description. Birch tar oil is obtained by the destructive distillation of the wood and bark of the silver birch, *Betula verrucosa* (*B. pendula*; *B. alba*), and the birch, *B. pubescens* (Betulaceae); the distillate is allowed to stand and the oily upper layer separated from the residual tar.

Cade Oil

Alquitrán de Enebro; Ardıç Katranı; Brea de enebro; Goudron de Cade; Juniper Tar; Juniper Tar Oil; Kad Yağı; Kadeöl; Oleum Cadinum; Oleum Juniperi Empyreumaticum; Pix Cadi; Pix Juniperi; Pix Oxycedri; Pyroleum Juniperi; Pyroleum Oxycedri; Wacholderteer; Можжевеловый Дёготь.
ATC Herb — HD05AA5001 (Juniperus oxycedrus: *tar*).
UNII — 1Q84T0P2G3.

Description. Cade oil contains guaiacol, ethylguaiacol, creosol, and cadinene.

Pharmacopoeias. In *US.*

USP 36: (Juniper Tar). The empyreumatic volatile oil obtained from the woody portions of *Juniperus oxycedrus* (Pinaceae). It is a dark brown, clear, thick liquid with a tarry odour. Very slightly soluble in water; soluble 1 in 9 of alcohol; soluble 1 in 3 of ether leaving only a slight flocculent residue; partially soluble in petroleum spirit; miscible with amyl alcohol, with chloroform, and with glacial acetic acid. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Coal Tar

Alcatrão Mineral; Alquitrán de hulla; Brea de hulla; Crude Coal Tar; Goudron de Houille; Kamenouhelný dehet; Katran; Oleum Lithanthracis; Pix Carbon.; Pix Carbonis; Pix Lithanthracis; Pix Mineralis; Pyroleum Lithanthracis; Steinkohlenteer; Каменноугольная Смола.
UNII — R533ESO2EC.

Description. Prepared coal tar is commercial coal tar heated at 50 degrees for 1 hour.

Alcoholic solutions of coal tar or prepared coal tar prepared with the aid of polysorbate have been referred to as Liquor Picis Carbonis and Liquor Carbonis Detergens.

Pharmacopoeias. In *Br., Fr., Int.,* and *US.*

BP 2014: (Coal Tar). A product obtained by the destructive distillation of bituminous coal at a temperature of about 1000 degrees. A nearly black, viscous liquid with a strong characteristic penetrating odour. On exposure to air it gradually becomes more viscous. It burns in air with a luminous sooty flame. Slightly soluble in water; partly soluble in absolute alcohol, in chloroform, in ether, and in volatile oils. A saturated solution is alkaline to litmus.

USP 36: (Coal Tar). The tar obtained by the destructive distillation of bituminous coal at temperatures in the range of 900 degrees to 1100 degrees. It may be processed further either by extraction with alcohol and suitable dispersing agents and maceration times or by fractional distillation with or without the use of suitable organic solvents.

A nearly black, viscous liquid with a characteristic naphthalene-like odour. Slightly soluble in water to which it imparts an alkaline reaction; partially soluble in alcohol, in acetone, in carbon disulfide, in chloroform, in ether, in methyl alcohol, and in petroleum spirit; more soluble in benzene; almost completely soluble in nitrobenzene. Store in airtight containers.

Tar

Alquitrán Vegetal; Brea; Brea de Pino; Brea vegetal; Goudron Végétal; Nadelholzteer; Pine Tar; Pix Abietinarum; Pix Liquida; Pix Pini; Pyroleum Pini; Wood Tar; Древесная Смола; Древесный Дёготь.
ATC Herb — HD08AW5002 (Pinus spp.: *tar*).
UNII — YFH4WC535J.

Pharmacopoeias. In *Br.*

BP 2014: (Tar). A bituminous liquid obtained from the wood of various trees of the family Pinaceae by destructive distillation. It is known in commerce as Stockholm Tar. A dark brown or nearly black semi-liquid with a characteristic empyreumatic odour; it is heavier than water. Soluble in alcohol (90%), in chloroform, in ether, and in fixed and volatile oils. The aqueous liquid obtained by shaking 1 g with 20 mL of water for 5 minutes is acidic to litmus paper.

Storage. When stored for some time tar separates into a layer which is granular in character due to minute crystallisation of catechol, resin acids, etc. and a surface layer of a syrupy consistence.

Uses and Administration

Tars and tar oils can reduce the thickness of the epidermis. They are antipruritic and may be weakly antiseptic. They are used topically in eczema (p. 1684.1), psoriasis (below), dandruff, seborrhoeic dermatitis (p. 1689.1), and other skin disorders. Coal tar preparations have largely replaced the use of wood tars. Ultraviolet (UVB) light increases the efficacy of coal tar in the treatment of psoriasis.

Some wood tars, including creosote (p. 1659.3) have been used in expectorant preparations.

Nonprescription use. After a review of products for safety and efficacy the FDA ruled that cade oil or tar should not be used in nonprescription shampoos[1] and that tar should no longer be included in nonprescription expectorants.[2]

1. Anonymous. Nonprescription drug review gains momentum. *WHO Drug Inf* 1991; 5: 62.
2. Anonymous. FDA announces standards for nonprescription sleep-aid products and expectorants. *Clin Pharm* 1989; 8: 388.

Psoriasis. Coal tar has long been employed in the treatment of psoriasis (p. 1688.1), and used alone or with dithranol and/or ultraviolet light it continues to be a first-line option, although its use is declining. It is particularly suited to the treatment of stable chronic plaque psoriasis. Its mode of action is unknown but it is considered to have antiproliferative and anti-inflammatory activity, producing a reduction in the thickness of viable epidermis. Crude tar preparations are rather messy and unpleasant; refined products may be more aesthetically acceptable and less likely to stain skin, hair, and clothing although some consider them to be less effective.

Treatments usually start with concentrations equivalent to 0.5 to 1% of crude coal tar with the concentration being increased as necessary every few days up to a maximum of 10%. The higher strength preparations may be required for the management of thicker patches of psoriasis but the British Association of Dermatologists considers that coal tar preparations of between 1 and 5% in white or yellow soft paraffin are as effective as higher concentrations, and that the use of higher concentrations, which has been traditionally advocated, has no evidence-based foundation and is best avoided, especially as it restricts outpatient use.

Coal tar may not clear psoriasis as fast as other agents but extended periods of remission can be obtained with its use. The Goeckerman regimen utilises the enhanced efficacy obtained when coal tar is applied before exposure to ultraviolet (UVB) light. The mechanism for this effect is unknown but it does not appear to be due to the photosensitising action of coal tar. In most regimens the coal tar is applied 2 hours before exposure to UVB light. In Ingram's regimen and its modifications the use of coal tar and UVB light is followed by topical treatment with dithranol. It has been suggested that the irritant effects of dithranol treatment can be reduced without loss of efficacy if coal tar is also used.

References.

1. Rotstein H, Baker C. The treatment of psoriasis. *Med J Aust* 1990; 152: 153–64.
2. Arnold WP. Tar. *Clin Dermatol* 1997; 15: 739–44.
3. Thami GP, Sarkar R. Coal tar: past, present and future. *Clin Exp Dermatol* 2002; 27: 99–103.
4. British Association of Dermatologists. Psoriasis – general management. Available at: http://www.bad.org.uk/site/769/Default.aspx (accessed 25/05/10)

Adverse Effects and Precautions

Tars and tar oils may cause irritation and acne-like eruptions of the skin and should not be applied to inflamed or broken skin, mucosa, or the anogenital area. They should be used with caution on the face and skin flexures. Hypersensitivity reactions are rare but wood tars are more likely to cause

sensitisation than coal tar. However, unlike wood tars, coal tar has a photosensitising action. Preparations of refined tar products appear to be less likely than crude tars to stain the skin, hair, and clothing.

Depending on their composition the systemic effects of tars and tar oils are similar to those for phenol (see p. 1764.2).

Carcinogenicity. Coal tar and coal tar distillates contain several known and potential carcinogens including benzene, naphthalene, and other polycyclic aromatic hydrocarbons.[1] Studies of occupational exposure (for example, during coke production, coal gasification, and aluminium production) have found systemic absorption of significant amounts of polycyclic aromatic hydrocarbons,[2] and increases in the risks of developing a range of cancers.[1,2] Systemic absorption of polycyclic aromatic hydrocarbons has also been measured after the application of coal tar preparations used in the treatment of skin conditions.[2] However, although an increased risk of skin carcinoma was found[3] in 59 patients with psoriasis who had had very high exposures to tar and/or UV radiation, other cohort studies[4-6] found no increase in the risk of developing cancers from coal tar, even after long-term use.

1. National Toxicology Program. Coal tars and coal tar pitches. *Rep Carcinog* 2002; **10**: 68–70.
2. van Schooten F-J, Godschalk R. Coal tar therapy: is it carcinogenic? *Drug Safety* 1996; **15**: 374–7.
3. Stern RS, *et al.* Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1980; **i**: 732–5.
4. Pittelkow MR, *et al.* Skin cancer in patients with psoriasis treated with coal tar. *Arch Dermatol* 1981; **117**: 465–8.
5. Jones SK, *et al.* Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 1985; **113**: 97–101.
6. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. *Cancer* 1994; **73**: 2759–64.

Extemporaneous preparation. Concern about the possible carcinogenic potential of coal tar (see above) led the Health and Safety Executive in the UK to recommend that gloves for chemical protection, as opposed to disposable surgeon's gloves, should be worn during the extemporaneous preparation of formulations containing coal tar.[1]

1. Anonymous. Chemical protection gloves recommended for coal tar ointments. *Pharm J* 1997; **259**: 757.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Alcoderm; Fijacid; Ingeshampt; Luxofar; Soriacur; Sorial; Sutrico Tar; Targel; *Austral.*: Alphosyl†; Linotar†; Neutrogena T/Gel; Pinetarsol; Polytar Plus; *Braz.*: Tarflex; Theratar; *Canad.*: Balnetar†; Doak-Oil; Exorex; Mazon Medicated Soap; Neutrogena T/Gel Therapeutic; Neutrogena T/Gel†; Pentrax; Psoriasin; T/Gel Therapeutic; Targel; Tersa-Tar; *Chile*: DHS Tar Gel; Neutrogena Shampoo Neutar†; Tarmed; Tigel Coaltar; *Cz.*: Delatar†; *Fr.*: Caditar; *Ger.*: Lorinden Teersalbe; Tarmed; Teer-Linola-Fett; *Gr.*: Exorex; Ionil; Neutrogena T/Gel; Tarmed; *Hong Kong*: Pinetarsol; Zetar†; *Hung.*: Freederm Tar Shampoo; *India*: Cotar; Exorex; *Irl.*: Exorex; Neutrogena T/Gel; Pentrax; Pinetarsol†; Psoriderm; *Israel*: Alphosyl 2 in 1; T/Gel†; *Ital.*: Konor; SDE Tar; *Malaysia*: Baby Shield Medicated Cleanser; Pin-Xol; Pinetarsol; *Mex.*: Ionil-T Plus†; Tarmed; *Neth.*: Exorex; *NZ*: Pinetarsol; *Pol.*: Delatar†; Freederm Tar†; Polytar; *Port.*: Neutar†; Tarmed; *Rus.*: Freederm Tar (Фрадерм Деготь); *S.Afr.*: Alphosyl†; Denorex; Exarex; Linotar†; *Singapore*: Hi-Tar; Pinetarsol; Polytar Plus; *Spain*: Alfitar; Alphosyl†; Exorex; Piroxgel; Tar Isdin Champu†; Tarmed; *UK*: Alphosyl 2 in 1; Carbo-Dome; Clinitar†; Exorex; Pentrax; Pinetarsol†; Psoriderm; T/Gel; *USA*: Balnetar; DHS Tar; Fototar; Grandpas Wonder Pine Tar Conditioner; Ionil-T Plus†; MG217 Medicated; Neutrogena T/Gel; Oxipor VHC; PC-Tar; Pentrax; Polytar; Psorent; Taraphilic; Tegrin; Tera-Gel; Zetar; *Venez.*: Neutrogena T-Gel.

Multi-ingredient Preparations. *Arg.*: Acnetrol; Aeroseb; Champuacid; Cidermex; Cremsor N; Eurocoal; Farm-X; Hyaluron; Ingemet†; Ionil-T; Laurinol Plus; Medic; Mencogrin AP; Mencogrin; Mencogrin; Novofarma; Novofarma; Novofarma; Oilalfo Compuesto; Salpad T; Sequals G; Sorsis Beta; Sorsis; Sorsis; *Austral.*: Alphosyl†; Eczema Cream; EgoPsoryl TA; Fongitar†; Hamilton Pine Tar with Menthol; Ionil-T; Pinetarsol; Pinetarsol; Polytar; Psor-Asist; Sebitar; *Braz.*: Hebrin; Ionil-T; Polytar; *Canad.*: Dan-Tar Plus†; Denorex Medicated; Herbal Multi-Tar Plus; Mazon Medicated Cream; Mazon Medicated Shampoo; Medi-Dan; Mild Multi-Tar Plus; Multi-Tar Plus†; Oxiport†; P & S Plus†; Polytar AP; Polytar; Regular Multi-Tar Plus; Sebcur-T; SJ Liniment†; Sterex Plus†; Sterex†; Tardan; Targel SA; X-Seb T Plus; X-Seb T; X-Tar†; *Chile*: Ionil-T; *Cz.*: Polytar AP; Polytar; Suspensio Visnevski cum Pice Liquida HBF; *Fr.*: Alkotar†; Lacoderme a l'huile de cade†; Node DS+; Node DS; Node K; Node P†; Novophane K; Psocortene†; Sebosquam†; Squaphane E; Squaphane P; Squaphane S; Squaphane; Squaphane; *Gr.*: Locacorten Tar; Pisaveril; *Hong Kong*: BP-2-4-2†; Egopsoryl TA; Fongitar; Ionil-T; Multi-Tar†; Polytar Emollient; Polytar; Sebitar; *Hung.*: Polytar AF†; Polytar†; *India*: Alphosyl; Carel; Coalsyl-S; Coalsyl-S; Cotar-K; Cotar-S; Dermatar; Derobin-HC; Derobin; Ionax T; Ketotar; Ocona-CT; *Indon.*: Polytar†; *Irl.*: Capasal; Cocois; Denorex†; Polytar Emollient; Polytar; Pragmatar†; *Israel*: Capasal; Polytar; *Ital.*: Listerine Tartar Control; Pentrax; Rivescal Tar; *Malaysia*: Egopsoryl TA; Mentar; Polytar; Sebitar; *Mex.*: Antaderm; Dariseb; Dealan; Dermoscalp; Ionil-T†; Jabon del Tio Nacho; Polytar; Sebryl Plus; Sebryl; Sebstopp; Shampoo del Tio Nacho†; *Mon.*: Dermagor Betacade; *Neth.*: Denorex; *NZ*: Coco-Scalp; Egopsoryl TA; Ionil-T; Polytar Emollient†; Polytar Plus; Polytar; Sebitar; *Philipp.*: Fongitar; Ionil-T†; Polytar; *Pol.*: Cocois; Polytar AP; Psorisan†; *Port.*: Alpha Cade; Banholeum Composto; Betacade; Fongitar; Polytar; *S.Afr.*: Alphosyl†; Fongitar; Haarlemensis; Oxipor VHC†; Polytar; SB Universal Ointment†; Tritar; *Singapore*: Cocois Co; Cocois; Egopsoryl TA; Fongitar; Ionil-T; Polytar; Sebitar; *Spain*: Alphosyl†; Emolytar†; Ionil Champu; Polytar†; Tar Isdin Plus†; Zincation Plus; *Thai.*: Fongitar†; Polytar; *Turk.*: Kadolin; Wilkinson†; *UK*: Alphosyl HC†; Capasal; Cocois; Polytar AF†; Polytar Emollient; Polytar Liquid; Polytar Plus; Psorin; Sebco; Snowfire; Varicose Ointment; *Ukr.*: Olesan (Олесан)†; *USA*: Ala seb T; Boil Ease; Ionil-T; Medotar; Neutrogena T/Sal; Pazol XS; Sal-Oil-T; Sebex-T; Tarlene; Tarsum; X-Seb T Plus; X-Seb T.

Homoeopathic Preparations. *Canad.*: Adrisin†.

Pharmacopoeial Preparations

BP 2014: Calamine and Coal Tar Ointment; Coal Tar and Salicylic Acid Ointment; Coal Tar and Zinc Ointment; Coal Tar Paste; Coal Tar Solution; Strong Coal Tar Solution; Zinc and Coal Tar Paste; USP 36: Coal Tar Ointment; Coal Tar Topical Solution; Compound Resorcinol Ointment.

Tazarotene *(BAN, USAN, rINN)*

AGN-190168; Tatsaroteeni; Tazaroten; Tazarotène; Tazarotenо; Tazarotenum; Тазаротен.

Ethyl 6-[(4,4-dimethylthiochroman-6-yl)ethynyl]nicotinate.

$C_{21}H_{21}NO_2S$=351.5

CAS — 118292-40-3.

ATC — D05AX05.

ATC Vet — QD05AX05.

UNII — 81BDR9Y8PS.

Uses and Administration

Tazarotene is a retinoid used for the topical treatment of mild to moderate acne and plaque psoriasis, and to treat signs of photoageing. Tazarotene is a prodrug that is de-esterified in the skin to its active form, tazarotenic acid. The mode of action is unknown but it appears to modulate cell proliferation and differentiation.

In the treatment of **psoriasis**, tazarotene 0.05% cream or gel is used initially and increased to 0.1% if necessary. It is applied once daily in the evening. In the UK tazarotene is licensed for use in patients with psoriasis affecting up to 10% of the body-surface; in the USA, it may be used on psoriasis involving up to 20% of the body-surface.

In the treatment of **acne**, tazarotene is applied as a 0.1% gel or cream once daily in the evening.

There may be exacerbation of acne during early treatment or of psoriasis at any time during treatment. The treatment period is usually up to 12 weeks, although tazarotene has been used for up to 12 months in the treatment of psoriasis.

A 0.1% cream is used in the topical treatment of certain signs of **photoageing** (facial fine wrinkling, mottled hypo- and hyperpigmentation, and benign facial lentigines). It is applied once daily at bedtime to lightly cover the entire face.

Reviews.

1. Foster RH, *et al.* Tazarotene. *Drugs* 1998; **55**: 705–11.
2. Tang-Liu DD-S, *et al.* Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. *Clin Pharmacokinet* 1999; **37**: 273–87.
3. Guenther LC. Optimizing treatment with topical tazarotene. *Am J Clin Dermatol* 2003; **4**: 197–202.

Malignant neoplasms. There has been some interest in the use of topical tazarotene in the treatment of neoplasms affecting the skin. Preliminary studies have reported some lesion regression or clearance in basal cell[1] and squamous cell carcinomas[2] (p. 714.2), and mycosis fungoides[3] (p. 698.3).

1. Bianchi L, *et al.* Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. *Br J Dermatol* 2004; **151**: 148–56.
2. Bardazzi F, *et al.* A pilot study on the use of topical tazarotene to treat squamous cell carcinoma in situ. *J Am Acad Dermatol* 2005; **52**: 1102–4.
3. Apisarnthanarax N, *et al.* Tazarotene 0.1% gel for refractory mycosis fungoides lesions: an open-label pilot study. *J Am Acad Dermatol* 2004; **50**: 600–607.

Skin disorders. Tazarotene is used for the topical treatment of mild to moderate acne[1,2] (p. 1682.2) and plaque psoriasis[3,4] (p. 1688.1); benefit has also been reported for psoriasis of the nails.[5,6] Improvement has been reported too in keratinisation disorders such as Darier's disease[7,8] (p. 1683.2) and congenital ichthyosis[9-11] (p. 1685.1). Topical tazarotene can also improve some signs of photoageing (p. 1686.2), including fine wrinkling, mottled hyperpigmentation, and lentigines (liver spots).[12-14]

1. Leyden JJ. Meta-analysis of topical tazarotene in the treatment of mild to moderate acne. *Cutis* 2004; **74** (4 suppl): 9–15.
2. Shalita AR, *et al.* Effects of tazarotene 0.1% cream in the treatment of facial acne vulgaris: pooled results from two multicenter, double-blind, randomized, vehicle-controlled, parallel-group trials. *Clin Ther* 2004; **26**: 1865–73.
3. Weinstein GD, *et al.* Tazarotene cream in the treatment of psoriasis: two multicenter, double-blind, randomized, vehicle-controlled studies of the safety and efficacy of tazarotene creams 0.05% and 0.1% applied once daily for 12 weeks. *J Am Acad Dermatol* 2003; **48**: 760–7.
4. Dando TM, Wellington K. Topical tazarotene: a review of its use in the treatment of plaque psoriasis. *Am J Clin Dermatol* 2005; **6**: 255–72.
5. Scher RK, *et al.* Tazarotene 0.1% gel in the treatment of fingernail psoriasis: a double-blind, randomized, vehicle-controlled study. *Cutis* 2001; **68**: 355–8.
6. Bianchi L, *et al.* Tazarotene 0.1% gel for psoriasis of the fingernails and toenails: an open, prospective study. *Br J Dermatol* 2003; **149**: 207–.
7. Oster-Schmidt C. The treatment of Darier's disease with topical tazarotene. *Br J Dermatol* 1999; **141**: 603–4.
8. Brazzelli V, *et al.* Linear Darier's disease successfully treated with 0.1% tazarotene gel "short-contact" therapy. *Eur J Dermatol* 2006; **16**: 59–61.
9. Hofmann B, *et al.* Effect of topical tazarotene in the treatment of congenital ichthyosis. *Br J Dermatol* 1999; **141**: 642–6.
10. Marulli GC, *et al.* Type I lamellar ichthyosis improved by tazarotene 0.1% gel. *Clin Exp Dermatol* 2003; **28**: 391–3.
11. Kundu RV, *et al.* Lamellar ichthyosis treated with tazarotene 0.1% gel. *J Am Acad Dermatol* 2006; **55** (suppl 5): S94–S95.
12. Phillips TJ, *et al.* Efficacy of 0.1% tazarotene cream for the treatment of photodamage: a 12-month multicenter, randomized trial. *Arch Dermatol* 2002; **138**: 1486–93.
13. Machtinger LA, *et al.* Histological effects of tazarotene 0.1% cream vs. vehicle on photodamaged skin: a 6-month, multicentre, double-blind, randomized, vehicle-controlled study in patients with photodamaged facial skin. *Br J Dermatol* 2004; **151**: 1245–52.
14. Kang S, *et al.* A multicenter, randomized, double-blind trial of tazarotene 0.1% cream in the treatment of photodamage. *J Am Acad Dermatol* 2005; **52**: 268–74.

Adverse Effects and Precautions

As for Tretinoin, p. 1726.1 and p. 1726.3.

Systemic absorption from tazarotene applied topically is low, and the most frequent adverse effects are on the skin; the incidence of adverse events appears to be concentration related.

Animal studies have indicated that tazarotene is fetotoxic and teratogenic. Licensed product information recommends that tazarotene should not be used during pregnancy or in women planning a pregnancy; it also advises starting therapy during normal menstruation, within 2 weeks of confirming a negative pregnancy test in women of child-bearing potential. Similarly, tazarotene should not be used, or used with caution, during breast feeding, as *animal* data indicate that it may be distributed into breast milk.

Effects on the skin. A 57-year-old man with diabetes and recalcitrant psoriasis on the trunk and limbs developed acute dermatitis[1] in the genital area 2 weeks after starting treatment with topical tazarotene 0.1%. The affected area became ulcerated over the next few days. It was suspected that accidental contact with the tazarotene that had been applied to the truncal psoriasis was responsible. Pyogenic granuloma has been associated with topical tazarotene and other retinoids given orally or applied topically (see Effects on the Skin, Hair, and Nails, under Isotretinoin, p. 1709.1).

1. Wollina U. Genital ulcers in a psoriasis patient using topical tazarotene. *Br J Dermatol* 1998; **138**: 713–14.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Zorac; *Austria*: Zorac; *Belg.*: Zorac; *Canad.*: Tazorac; *Chile*: Aguder; *China*: Le Wei (乐维); Que Wei (炔维); *Cz.*: Tazorac†; *Fr.*: Zorac; *Gr.*: Zorac; *India*: A-Ret TZ; La Tez; Tazret; *Irl.*: Zorac†; *Israel*: Zorac; *Ital.*: Zorac; *Mex.*: Suretin; Tazmeral; *Pol.*: Zorac; *S.Afr.*: Zorac; *Singapore*: Avage; *Spain*: Zorac; *Switz.*: Zorac†; *UK*: Zorac; *USA*: Avage; Fabior; Tazorac.

Thioglycollic Acid

Kwas tioglikolowy; Tioglicólico, ácido; Тиогликолевая кислота.

Mercaptoacetic acid.

$C_2H_4O_2S$=92.11

CAS — 68-11-1.

UNII — 7857H94KHM.

Calcium Thioglycollate

Calcium Mercaptoacetate; Tioglicolato cálcico; Тиогликолят кальция.

Calcium mercaptoacetate trihydrate.

$C_2H_2CaO_2S,3H_2O$=184.2

CAS — 814-71-1.

UNII — J96129652N (calcium thioglycollate); F376WF95N7 (calcium thioglycollate trihydrate).

Profile

Thioglycollic acid is used, usually as the calcium salt, in depilatory preparations. Thioglycollates are also used in hair waving or straightening products with potassium bromate

as the neutraliser. There have been reports of skin reactions associated with the use of thioglycollates.

Tioxolone *(BAN, rINN)*

OL-110; Thioxolone; Tioksolon; Tioksoloni; Tioxolon; Tioxolona; Tioxolonum; Тиоксолон.
6-Hydroxy-1,3-benzoxathiol-2-one.
$C_7H_4O_3S$=168.2.
CAS — 4991-65-5.
ATC — D10AB03.
ATC Vet — QD10AB03.
UNII — S0FAJ1R9CD.

Pharmacopoeias. In *Pol.*

Profile

Tioxolone has astringent and keratolytic effects, and has been used topically in the treatment of various skin and scalp disorders.

Titanium Dioxide

CI Pigment White 6; Colour Index No. 77891; E171; Oxid titaničitý; Titaanidioksidi; Titandioxid; Titán-dioxid; Titane, dioxyde de; Titanii dioxidum; Titanio, dióxido de; Titanium Oxide; Titano dioksidas; Titanyum Dioksit; Tytanu(IV) tlenek; Диоксид Титана; Двуокись Титана.
TiO_2=79.86.
CAS — 13463-67-7.
UNII — 15FIX9V2JP.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Titanium Dioxide). A white or almost white powder. Practically insoluble in water; it does not dissolve in dilute mineral acids but dissolves slowly in hot concentrated sulfuric acid.

USP 36: (Titanium Dioxide). A white odourless powder. Insoluble in water, in hydrochloric acid, in nitric acid, and in 2N sulfuric acid; dissolves in hot sulfuric acid and in hydrofluoric acid; it is rendered soluble by fusion with potassium bisulfate or with alkali hydroxides or carbonates. A 10% suspension in water is neutral to litmus.

Profile

Titanium dioxide has an action on the skin similar to that of zinc oxide (p. 1729.1) and has similar uses. Titanium peroxide and titanium salicylate are used with titanium dioxide for nappy rash. Titanium dioxide reflects ultraviolet light and is used as a physical sunscreen (p. 1681.3). It is also an ingredient of some cosmetics. It is used to pigment and opacify hard gelatin capsules and tablet coatings and as a delustring agent for regenerated cellulose and other man-made fibres. Specially purified grades may be used in food colours.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Sunsense Sensitive; *Canad.*: Aquasmooth†; Creme de Soins†; Dermalogica Ultra Sensitive Face Block†; Luxiva Lasting†; Neutrogena Sensitive Skin†; Photogenic Concealer†; Revlon Complexion One Step†; Stila†; *Chile*: Fotocrem P; Neutrogena Bloqueador Solar Piel Sensible†; Unitone 4; *Ger.*: Haemo-Exhirud Bufexamac†; *Hong Kong*: Sunsense Sun Sensitive; *Malaysia*: Sunsense Sunsensitive; *Mex.*: Blancaler; Uveil PS; *NZ*: Active Duty Sunscreen; Hamilton Sunscreen†; *Philipp.*: Innobloc; *Port.*: Dermagor Ecran Solar†; *Singapore*: Sunsense Sunsensitive; *USA*: Hawaiian Tropic Protective Tanning; Neutrogena Chemical-Free; TI Baby Natural; TI Screen Natural; Vanicream; *Venez.*: Uveil PS.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations
BP 2014: Titanium Ointment.

Trafermin *(USAN, rINN)* ⊗

CAB-2001; Trafermina; Trafermine; Trafferminum; Трафермин.
2-155-Basic fibroblast growth factor (human clone λKB7/λHFL1 precursor reduced).
CAS — 131094-16-1.

Profile

Trafermin is a human recombinant basic fibroblast growth factor (b-FGF) that promotes tissue granulation and the formation of new blood vessels. It is used as a topical liquid spray for the treatment of burns and intractable skin ulcers.

References.
1. Robson MC, *et al.* Sequential cytokine therapy for pressure ulcers: clinical and mechanistic response. *Ann Surg* 2000; 231: 600–11.
2. Payne WG, *et al.* Long-term outcome study of growth factor-treated pressure ulcers. *Am J Surg* 2001; 181: 81–6.
3. Ichioka S, *et al.* The positive experience of using a growth factor product on deep wounds with exposed bone. *J Wound Care* 2005; 14: 105–9.
4. Motomura H, *et al.* Aggressive conservative therapy for refractory ulcer with diabetes and/or arteriosclerosis. *J Dermatol* 2006; 33: 353–9.
5. Hashimoto N, *et al.* Management of skull base defect with bFGF after extensive skull base surgery — two case reports. *Minim Invasive Neurosurg* 2008; 51: 136–9.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Jpn*: Fiblast.

Tretinoin *(BAN, USAN, rINN)*

Acido retinoico; NSC-122758; Retinoic Acid; Tretinoilni; Tretinoína; Tretinoinas; Trétinoïne; Tretinoinum; Tretynoina; Vitamin A Acid; Vitamina A ácida; Третиноин.
all-trans-Retinoic acid; 13-*cis*-Retinoic acid; 15-Apo-β-caroten-15-oic acid; 3,7-Dimethyl-9-(2,6,6-trimethylcyclohex-1-enyl)nona-2,4,6,8-*all-trans*-tetraenoic acid.
$C_{20}H_{28}O_2$=300.4.
CAS — 302-79-4 (tretinoin); 40516-48-1 (tretinoin tocoferil).
ATC — D10AD01; L01XX14.
ATC Vet — QD10AD01; QL01XX14.
UNII — 5688UTC01R.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *US*.

Ph. Eur. 8: (Tretinoin). A yellow or light orange crystalline powder. Practically insoluble in water; slightly soluble in alcohol; sparingly soluble in dichloromethane. It is sensitive to light, heat, and air, especially in solution. Store in airtight containers under an inert gas. Protect from light. The contents of an opened container should be used as soon as possible and any unused portion should be protected by an atmosphere of an inert gas.

USP 36: (Tretinoin). A yellow to light-orange crystalline powder. Insoluble in water; slightly soluble in alcohol and in chloroform. Store in airtight containers, preferably under an atmosphere of an inert gas. Protect from light.

Uses and Administration

Tretinoin is a retinoid and is the acid form of vitamin A (p. 2098.3).

Tretinoin is mainly used in the topical treatment of **acne vulgaris** when comedones, papules, and pustules predominate. It appears to stimulate mitosis and turnover of follicular epithelial cells and reduce their cohesiveness thereby facilitating the extrusion of existing comedones and preventing the formation of new ones. It also appears to have a thinning effect on the stratum corneum. Tretinoin is applied as a cream, gel, or alcoholic solution, usually containing 0.01 to 0.1%. The skin should be cleansed to remove excessive oiliness and dried before applying tretinoin lightly, once or twice daily according to response and irritation; some patients may require less frequent applications. Other topical preparations (including skin moisturisers) should not be applied at the same time as tretinoin is applied, and caution is required if other local irritants are used concurrently. There may be apparent exacerbations of the acne during early treatment and a therapeutic response may not be evident for 6 to 8 weeks. When the condition has resolved maintenance therapy should be less frequent.

Preparations containing 0.02 or 0.05% tretinoin have been used for the treatment of mottled hyperpigmentation, roughness, and fine wrinkling of **photodamaged skin**. It is applied once daily at night. Effects may not be seen until about 6 months after starting treatment.

Tretinoin is also used to induce remission in acute promyelocytic **leukaemia**. A daily dose of 45 mg/m² is given orally in 2 divided doses with food. Treatment is continued until complete remission has occurred or up to a maximum of 90 days. Dose reduction has been recommended in hepatic or renal impairment (see below).

For the use of tretinoin in children, see below.

A liposomal formulation of tretinoin for intravenous use has been investigated in T-cell non-Hodgkin's lymphoma, and acute and chronic leukaemia.

Tretinoin tocoferil (tocoretinate) has also been used.

Administration in children. Topical tretinoin is licensed in the UK for acne vulgaris but the product information does not give age limits or specify any particular patient population. It is not licensed for infantile acne although the *BNFC* suggests that it may be used under specialist supervision.

The use of oral tretinoin to induce remission in acute promyelocytic leukaemia (see Malignant Neoplasms, below) in children has been studied.[1-3] Although there is less experience than in adults, a similar dosage regimen of 45 mg/m² daily (see also above) has been used in children ranging in age from 1 to 16 years. Dose reduction should be considered if severe toxicity, particularly intractable headache, occurs. Although a lower dose of 25 mg/m² daily might reduce neurotoxicity[2,3] the two doses have not been directly compared.

1. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; 22: 1404–12.
2. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; 106: 447–53.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; 23: 7632–40.

Administration in hepatic and renal impairment. Although dosage adjustment has not been studied in patients with hepatic or renal impairment, licensed UK product information suggests that oral doses of tretinoin for acute promyelocytic leukaemia should be reduced to 25 mg/m² daily.

There is a report[1] of 2 patients who required dialysis during tretinoin treatment for acute promyelocytic leukaemia and who achieved remission; one was given a dose of 20 mg/m² daily in 2 divided doses and the other received 35 mg/m² daily in 3 divided doses.

1. Takitani K, *et al.* Pharmacokinetics of all-trans retinoic acid in acute promyelocytic leukemia patients on dialysis. *Am J Hematol* 2003; 74: 147–8.

Malignant neoplasms. Tretinoin differentiation therapy has become the established treatment for acute promyelocytic leukaemia (APL), a subtype of acute myeloid leukaemia (p. 693.1). Tretinoin is effective in APL because the characteristic chromosomal abnormalities result in an abnormal retinoic acid receptor. When given *orally*, it has produced complete remissions in more than 90% of patients.[1-4] However, the duration of remission is short unless consolidation, usually with an anthracycline- and cytarabine-based regimen, is given concurrently or subsequently. The combination of tretinoin and chemotherapy has been shown to result in improved survival compared with chemotherapy alone.[1,5,6] Prolonged maintenance therapy including intermittent tretinoin also appears to reduce the rate of relapse.[6] Although benefit has been reported with continuous tretinoin maintenance[7] this is generally considered to lead to resistance.[8] A life-threatening syndrome has developed in some patients who have received oral tretinoin for APL (see Retinoic Acid Syndrome, under Adverse Effects, p. 1726.2). Children seem particularly sensitive to the adverse effects of oral tretinoin on the CNS (see also Effects on the Eyes, p. 1726.1, and Administration in Children, above). A lipid-based *intravenous* formulation of tretinoin has been investigated for the treatment of APL.

Tretinoin has also been tried for *topical* chemoprevention in patients at increased risk of skin cancers, and in the management of oral leucoplakia (see Malignant Neoplasms under Isotretinoin, p. 1707.1).

1. Avvisati G, Tallman MS. All-trans retinoic acid in acute promyelocytic leukaemia. *Best Pract Res Clin Haematol* 2003; 16: 419–32.
2. de Botton S, *et al.* Outcome of childhood acute promyelocytic leukemia with all-trans-retinoic acid and chemotherapy. *J Clin Oncol* 2004; 22: 1404–12.
3. Ortega JJ, *et al.* Treatment with all-trans retinoic acid and anthracycline monochemotherapy for children with acute promyelocytic leukemia: a multicenter study by the PETHEMA Group. *J Clin Oncol* 2005; 23: 7632–40.
4. Testi AM, *et al.* GIMEMA-AIEOP AIDA protocol for the treatment of newly diagnosed acute promyelocytic leukemia (APL) in children. *Blood* 2005; 106: 447–53.
5. Tallman MS, *et al.* Acute promyelocytic leukemia: evolving therapeutic strategies. *Blood* 2002; 99: 759–67.
6. Tallman MS, Nabhan C. Management of acute promyelocytic leukemia. *Curr Oncol Rep* 2002; 4: 381–9.
7. Tallman MS, *et al.* All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American Intergroup protocol. *Blood* 2002; 100: 4298–4302.
8. Fenaux P, *et al.* A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. *Blood* 1999; 94: 1192–1200.

Skin disorders. Topical treatment with tretinoin has been tried with varying success in many cutaneous conditions. Its use in acne (p. 1682.2) is well established. Some benefit has also been reported in rosacea[1] (p. 1688.3), in keratinisation disorders such as Darier's disease (p. 1683.2), and in pigmentation disorders (p. 1687.2) such as chloasma.[2] Healing of diabetic foot ulcers (see Diabetic Foot Disease, p. 464.2) was improved in a small placebo-controlled study of topical tretinoin.[3] The 0.05% solution was applied topically for 10 minutes of every day for 4 weeks.

Topical tretinoin is used to improve some of the signs of photoageing (p. 1686.2). Studies have found that tretinoin can improve fine facial wrinkling, with some reduction in coarse wrinkles, tactile roughness, sallowness, irregular pigmentation, and actinic lentigines.[4-6] Tretinoin appears to

prevent and repair collagen damage and reduce epidermal melanin content; there is also increased epidermal proliferation and thickening, compaction of the stratum corneum, and deposition of mucinous material.[5] The previous suggestion that skin irritation might be the mechanism behind tretinoin's effects on photodamaged skin has not been supported by clinical study.[4,5] It can take up to 4 months of treatment for a response to develop and the maximum response can be reached between 8 and 12 months. Continued use is necessary to maintain the effect of tretinoin, although it may be used less often.[5,6]

1. Ertl GA, *et al.* A comparison of the efficacy of topical tretinoin and low-dose oral isotretinoin in rosacea. *Arch Dermatol* 1994; 130: 319–24.
2. Griffiths CEM, *et al.* Topical tretinoin (retinoic acid) improves melasma: a vehicle-controlled, clinical trial. *Br J Dermatol* 1993; 129: 415–21.
3. Tom WL, *et al.* The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes. *Arch Dermatol* 2005; 141: 1373–7.
4. Griffiths CEM. The role of retinoids in the prevention and repair of aged and photoaged skin. *Clin Exp Dermatol* 2001; 26: 613–18.
5. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. *Drugs* 2005; 65: 1061–72.
6. Singh M, Griffiths CEM. The use of retinoids in the treatment of photoaging. *Dermatol Ther* 2006; 19: 297–305.

Adverse Effects

Tretinoin is a skin irritant. Topical application may cause transitory stinging and a feeling of warmth, and in normal use it produces some erythema, dryness, pruritus, and peeling similar to that of mild sunburn. Sensitive individuals may have oedema, blistering, and crusting of the skin. Excessive application can cause severe erythema, peeling, and discomfort with no increase in efficacy. Photosensitivity may occur. Temporary hypopigmentation and hyperpigmentation have been reported.

Oral doses of tretinoin may produce similar adverse effects to those of isotretinoin (see p. 1707.2). Adverse cardiovascular effects have also been reported; the most common were arrhythmias, flushing, hypotension, hypertension, and heart failure. Less common events were cardiac arrest, myocardial infarction, cardiomegaly, heart murmur, ischaemia, stroke, myocarditis, pericarditis, pulmonary hypertension, and secondary cardiomyopathy. A potentially life-threatening 'retinoic acid syndrome' (see below) has been described after oral use.

References.

1. Geng A, *et al.* Tolerability of high-dose topical tretinoin: the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Br J Dermatol* 2009; 161: 918–24.

Carcinogenicity. Studies in *mice* suggested that tretinoin could enhance photocarcinogenesis.[1] However, other studies refuted this[2] and evidence indicates that topical tretinoin is not carcinogenic in humans.

1. Epstein JH. Chemicals and photocarcinogenesis. *Australas J Dermatol* 1977; 18: 57–61.
2. Epstein JH. All-trans-retinoic acid and cutaneous cancers. *J Am Acad Dermatol* 1986; 15: 772–8.

Effects on the blood. Transient and asymptomatic thrombocytosis has been reported with the use of oral tretinoin, see under Isotretinoin, p. 1707.3.

Effects on the cardiovascular system. Tretinoin given for induction remission rapidly improves the coagulopathy associated with acute promyelocytic leukaemia, but there are associated reports of arterial and venous thromboembolism. In some cases the combination of tretinoin with an antifibrinolytic drug such as tranexamic acid may have increased the risk of thrombosis.[1-3] In other cases,[2,4] thrombosis occurred in the absence of tranexamic acid and appeared to be related to the retinoic acid syndrome (below). An assessment of 124 patients, including 11 who developed thrombosis, found that the expression of particular phenotypic and genotypic features of leukaemic cells may indicate an increased risk of thrombotic events in patients given tretinoin.[5]

For reports associated with other retinoids, see under Isotretinoin, p. 1707.3.

1. Brown JE, *et al.* All-trans retinoic acid (ATRA) and tranexamic acid: a potentially fatal combination in acute promyelocytic leukaemia. *Br J Haematol* 2000; 110: 1010–12.
2. Goldschmidt N, *et al.* Extensive splenic infarction, deep vein thrombosis and pulmonary emboli complicating induction therapy with all-trans-retinoic acid (ATRA) for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; 44: 1433–7.
3. Levin M-D, *et al.* Acute renal cortex necrosis caused by arterial thrombosis during treatment for acute promyelocytic leukemia. *Haematologica* 2003; 88: ECR21. Available at: http://www.haematologica.org/cgi/reprint/88/6/ECR21.pdf (accessed 28/07/08)
4. Torromeo C, *et al.* Intraventricular thrombosis during all-trans retinoic acid treatment in acute promyelocytic leukemia. *Leukemia* 2001; 15: 1311–13.
5. Breccia M, *et al.* Occurrence of thrombotic events in acute promyelocytic leukemia correlates with consistent immunophenotypic and molecular features. *Leukemia* 2007; 21: 79–83.

Effects on the eyes. Papilloedema, retinal haemorrhage and visual changes as a result of benign intracranial hypertension have been associated with oral tretinoin;[1] children appear to be particularly sensitive. For further information about oral retinoids, including tretinoin, causing benign intracranial hypertension, see Effects on the Eyes under Isotretinoin, p. 1707.3.

1. Mahmoud HH, *et al.* Tretinoin toxicity in children with acute promyelocytic leukaemia. *Lancet* 1993; 342: 1394–5.

Effects on the musculoskeletal system. For reports of myositis occurring in patients receiving oral tretinoin, see under Isotretinoin, p. 1708.2.

Effects on the nervous system. Neurotoxicity (ataxia, dysarthria, and headache) has been reported in a woman with liver impairment using topical tretinoin 0.025% for acne.[1]

1. Bernstein AL, Leventhal-Rochon JL. Neurotoxicity related to the use of topical tretinoin (Retin-A). *Ann Intern Med* 1996; 124: 227–8.

Effects on the skin. Painful scrotal ulcers, often accompanied by fever, have occurred in men receiving oral tretinoin for acute promyelocytic leukaemia.[1-5] The appearance of the ulcers ranged from days 9 to 30 of the tretinoin course and improved after it was stopped (either at complete remission or because of the ulceration or other adverse effects). Management of the ulcers often included an intravenous or topical corticosteroid and in some cases an antibacterial ointment. Genital ulcers have also been reported in 2 women;[3] an 8-year-old girl developed ulcers 5 days after finishing a course of tretinoin.[6]

Sweet's syndrome (acute febrile neutrophilic dermatosis) has been reported in at least 12 patients treated with oral tretinoin for acute promyelocytic leukaemia.[7] In some cases there was also systemic involvement affecting muscle, kidneys, and lungs, and in a few cases patients also had retinoic acid syndrome (below). Most patients responded to systemic corticosteroid treatment and in some cases the course of tretinoin therapy could be continued as a result. There has also been a report[8] of Sweet's syndrome with myalgia and arthralgia in a child treated with oral tretinoin for acute myeloid leukaemia.

Details of other skin reactions to oral and topical retinoids, including tretinoin, are described under Isotretinoin, p. 1709.1.

1. Mori A, *et al.* Scrotal ulcer occurring in patients with acute promyelocytic leukemia during treatment with all-trans retinoic acid. *Oncol Rep* 1999; 6: 55–8.
2. Charles KS, *et al.* Scrotal ulceration during all-trans retinoic (ATRA) therapy for acute promyelocytic leukaemia. *Clin Lab Haematol* 2000; 22: 171–4.
3. Fukuno K, *et al.* Genital ulcers during treatment with ALL-trans retinoic acid for acute promyelocytic leukemia. *Leuk Lymphoma* 2003; 44: 2009–13.
4. Gettinger S, *et al.* Scrotal ulceration during all-trans-retinoic acid therapy for acute promyelocytic leukemia. *J Clin Oncol* 2004; 22: 4648–9.
5. Shimizu D, *et al.* Scrotal ulcers arising during treatment with all-trans retinoic acid for acute promyelocytic leukemia. *Intern Med* 2005; 44: 480–3.
6. Ünal S, *et al.* Genital ulcers after treatment with all-trans-retinoic acid in a child with acute promyelocytic leukemia. *Pediatr Hematol Oncol* 2005; 22: 357–9.
7. Astudillo L, *et al.* Sweet's syndrome associated with retinoic acid syndrome in a patient with promyelocytic leukemia. *Ann Hematol* 2002; 81: 111–14.
8. Al-Saad K, *et al.* Sweet syndrome developing during treatment with all-trans retinoic acid in a child with acute myelogenous leukemia. *J Pediatr Hematol Oncol* 2004; 26: 197–9.

Retinoic acid syndrome. A syndrome consisting mainly of fever and respiratory distress developed in 9 of 35 patients between 2 and 21 days after starting induction therapy with oral tretinoin for suspected acute promyelocytic leukaemia.[1] Other symptoms included weight gain, oedema of the lower extremities, pleural or pericardial effusions, and episodic hypotension. Symptoms were life-threatening in 5 patients, 3 of whom subsequently died of multi-system failure. Leucocytosis was frequently, although not invariably, associated with development of the syndrome. Experience showed that early treatment with high-dose corticosteroids should be given to these patients irrespective of the leucocyte count. An analysis[2] of 739 patients has reported similar findings and suggested that, although controversial, prophylactic treatment with corticosteroids may reduce the incidence of the more severe form of the syndrome. Renal failure and pulmonary infiltrates occurred quite frequently in such patients and an association between severity of the syndrome and coagulopathy, and death caused by haemorrhage was noted. There have also been a few reports of thrombosis occurring with the retinoic acid syndrome (see Effects on the Cardiovascular System, above).

Reviews[3,4] and an analysis[2] of this syndrome, known as the 'retinoic acid syndrome' or 'differentiation syndrome', reported that it occurs in about 25% of patients with acute promyelocytic leukaemia treated with tretinoin and that the median time to onset is 10 to 12 days after the start of treatment; the severity of the syndrome varies greatly. A high leucocyte count at diagnosis or a rapidly-increasing count on initiation of therapy appears to increase the likelihood of the syndrome occurring. Close monitoring of leucocyte counts and clinical signs is recommended; high-dose intravenous corticosteroids, and possibly antineoplastic drugs, should be given if symptoms appear or the leucocyte count increases rapidly.

A similar syndrome has been reported in patients with acute promyelocytic leukaemia treated with arsenic trioxide (see p. 2448.3). A capillary leak syndrome, similar to retinoic acid syndrome, has also been described with acitretin (see p. 1691.2).

1. Frankel SR, *et al.* The "retinoic acid syndrome" in acute promyelocytic leukemia. *Ann Intern Med* 1992; 117: 292–6.
2. Montesinos P, *et al.* Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood* 2009; 113: 775–83.
3. Fenaux P, De Botton S. Retinoic acid syndrome: recognition, prevention and management. *Drug Safety* 1998; 18: 273–9.
4. Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best Pract Res Clin Haematol* 2003; 16: 45 l–61.

Vasculitic syndromes. For a report of vasculitis associated with oral tretinoin, see under Isotretinoin, p. 1709.2.

Precautions

Contact of tretinoin with the eyes, mouth, or other mucous surfaces should be avoided. It should not be applied to eczematous, sunburnt, or abraded skin and the effects of other topical treatment, especially with keratolytics, should be allowed to subside before topical use of tretinoin. Exposure to UV light and excessive exposure to sunlight should be avoided.

Absorption does not seem to occur to any great extent with topical use. Nevertheless, because of teratogenicity in *animal* studies and isolated cases of congenital abnormalities (see below), licensed product information suggests that the use of topical tretinoin should be avoided during pregnancy. It is unknown whether tretinoin is distributed into breast milk, and it should therefore be used topically with caution in breast-feeding mothers.

When tretinoin is given orally the precautions described under isotretinoin (see p. 1709.2) should be adopted. Oral tretinoin is contra-indicated in pregnancy and in breast feeding mothers.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies tretinoin as probably not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Pregnancy. Although there have been isolated reports[1-4] of congenital abnormalities in infants born to mothers who used tretinoin topically before and during pregnancy, studies involving a total of 415 women[5-7] showed no increased risk for major congenital disorders in infants who had been exposed in the first trimester.

As a characteristic pattern of fetal malformation has been described with the use of oral retinoids, particularly isotretinoin (see p. 1709.3), licensed product information warns that oral tretinoin is contra-indicated during pregnancy and that conception should be avoided for at least one month after the end of treatment. Nevertheless, the outcomes of up to 20 cases have been reviewed,[8,9] in which a course of tretinoin was generally given in the second or third trimester for promyelocytic leukaemia; some women were also given cytotoxic chemotherapy. There were reports of transient pulmonary and cardiac complications in some infants, but no congenital malformations were described. In one case[10] tretinoin was started in the first trimester and continued throughout the pregnancy to avoid the use of cytotoxic chemotherapy. The small-for-date infant was born by caesarean section at week 32 with jaundice and respiratory distress syndrome, which both resolved within 11 days. At 15 months of age the infant had normal growth and development.

1. Camera G, Pregliasco P. Ear malformation in baby born to mother using tretinoin cream. *Lancet* 1992; 339: 687.
2. Lipson AH, *et al.* Multiple congenital defects associated with maternal use of topical tretinoin. *Lancet* 1993; 341: 1352–3.
3. Navarre-Belhassen C, *et al.* Multiple congenital malformations associated with topical tretinoin. *Ann Pharmacother* 1998; 32: 505–6.
4. Colley SMJ, *et al.* Topical tretinoin and fetal malformations. *Med J Aust* 1998; 168: 467.
5. Jick SS, *et al.* First trimester topical tretinoin and congenital disorders. *Lancet* 1993; 341: 1181–2.
6. Shapiro L, *et al.* Safety of first-trimester exposure to topical tretinoin: prospective cohort study. *Lancet* 1997; 350: 1143–4.
7. Loureiro KD, *et al.* Minor malformations characteristic of the retinoic acid embryopathy and other birth outcomes in children of women exposed to topical tretinoin during early pregnancy. *Am J Med Genet* 2005; 136A: 117–21.
8. Giagounidis AAN, *et al.* Acute promyelocytic leukemia and pregnancy. *Eur J Haematol* 2000; 64: 267–71.
9. Consoli U, *et al.* Acute promyelocytic leukemia during pregnancy: report of 3 cases. *Int J Hematol* 2004; 79: 31–6.
10. Simone MD, *et al.* All-trans retinoic acid (ATRA) administration during pregnancy in relapsed acute promyelocytic leukemia. *Leukemia* 1995; 9: 1412–13.

Skin fragility. As with other retinoids (see under Isotretinoin, p. 1710.1) the use of depilatory products should be avoided in patients treated with tretinoin. Erosions of the skin occurred in 2 patients after the use of wax depilation on facial areas also being treated topically with tretinoin.[1]

1. Goldberg NS, Zalka AD. Retin-A and wax epilation. *Arch Dermatol* 1989; 125: 1717.

Interactions

As for Isotretinoin, p. 1710.1.

Tretinoin is metabolised by the hepatic cytochrome P450 isoenzyme system, therefore there is a potential for interaction between oral tretinoin and inhibitors or inducers of these enzymes.

Antifibrinolytics. Thrombotic events have occurred in patients being treated with tretinoin and *tranexamic acid* (see Effects on the Cardiovascular System, p. 1726.1). Licensed product information for tretinoin used in the treatment of acute promyelocytic leukaemia advises caution when it is given with drugs such as *aminocaproic acid, aprotinin,* and tranexamic acid, particularly in the first month of treatment.

Minoxidil. For the effect of tretinoin on the percutaneous absorption of minoxidil, see p. 1439.3.

Pharmacokinetics

After oral doses tretinoin is well absorbed from the gastrointestinal tract, and peak plasma concentrations occur after 1 to 2 hours. Oral bioavailability is about 50%. Systemic absorption is minimal after topical application. Tretinoin is highly bound to plasma proteins. It undergoes metabolism in the liver by the cytochrome P450 isoenzyme system. Metabolites include isotretinoin, 4-oxo-*trans*-retinoic acid, and 4-oxo-*cis*-retinoic acid. The terminal elimination half-life of tretinoin is 0.5 to 2 hours. Tretinoin is excreted in the bile and the urine. There is some evidence that tretinoin induces its own metabolism.

References.

1. Regazzi MB, *et al.* Clinical pharmacokinetics of tretinoin. *Clin Pharmacokinet* 1997; 32: 382–402.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: A Acido; Dorpiel; Eurotretin; Locacid; Lotioblanc; Neotretin; Niterey; Retacnyl; Reticne; Retin-A; Tretinoderm; Vesanoid; ***Austral.***: Retin-A†; ReTrieve; Stieva-A; Vesanoid; ***Austria***: Eudyna; Retin-A; Vesanoid; ***Belg.***: Vesanoid; ***Braz.***: Retin-A; Retinova†; Vesanoid; Vitacid; Vitanol-A; ***Canad.***: Rejuva-A; Renova; Retin-A; Retisol-A; Stieva-A; Vesanoid; ***Chile***: Dermodan; Retacnyl; Retin-A; Stieva-A; Vesanoid; ***China***: Ailike (艾力可); Di Wei (迪维); Li Ling (丽英); Wei Ai (唯爱); *Cz.*: Airol†; Locacid; Retin-A; Vesanoid; ***Fin.***: Avitcid; Vesanoid; ***Fr.***: Effederm; Ketrel; Locacid; Retacnyl; Retin-A†; Vesanoid; ***Ger.***: Airol; Cordes VAS; Vesanoid; ***Gr.***: Airol; Alfamatic; Retin-A; Vesanoid; ***Hong Kong***: Acta; Quali-A; Retin-A; ReTrieve; Stieva-A; Vesanoid; Vitamin A Acid†; ***India***: A-Ret; Airol; Comedolytic; Eudyna; Ontin; ***Indon.***: Eudyna; Jeraklin†; Melavita†; Nuface; Reticor; Retin-A; ReviDerm; Skinovit†; Tracne; Trentin; Vitacid; ***Irl.***: Retin-A; Vesanoid; ***Israel***: Airol†; Locacid; Retavit; Retin-A†; Vesanoid; ***Ital.***: Airol; Retin-A; Vesanoid; ***Jpn***: Olcenon; Vesanoid; ***Malaysia***: Alten†; Retacnyl; Retin-A; Stieva-A; T3 Actin; Tretinon; Vesanoid; ***Mex.***: Acnil; Arretin; Biovitol-C; Epitrel; Queratal; Reacel-A; Ret-A-Pres; Retacnyl; Retin-A; Stieva-A; Tocoderm; Vesanoid; ***Neth.***: Acid A Vit; Vesanoid; ***Norw.***: Aberela; ***NZ***: Retin-A; Retinova; ReTrieve; Vesanoid; ***Philipp.***: Airol†; Derm A; Retacnyl; Retin-A; Stieva-A; T3 Actin; Vesanoid; ***Pol.***: Arretin†; Atrederm; Locacid; Retin-A; Vesanoid; ***Port.***: Ketrel; Locacid; Retin-A; Vesanoid; ***Rus.***: Locacid (Локацид); Retin-A (Ретин-А); Vesanoid (Весаноид); ***S.Afr.***: Airol; Derma-T; Ilotycin-A; Renova; Retacnyl; Retin-A; Vesanoid; ***Singapore***: Alten†; Retacnyl; Retin-A; Retinova; ReTrieve; Stieva-A; T3 Actin; Vesanoid; ***Spain***: Dermojuventus†; Neocare; Retirides; Vesanoid; Vitanol†; ***Swed.***: Aberela; ***Switz.***: Airol; Retin-A; Vesanoid; ***Thai.***: Renova; Retacnyl; Retin-A; Stieva-A; Tina-A; Vesanoid; ***Turk.***: Acnelyse; Retino; Tretin; Vesanoid; ***UK***: Retin-A†; Vesanoid; ***Ukr.***: Vesanoid (Весаноид); ***USA***: Atralin; Avita; Refissa; Renova; Retin-A; Tretin-X; Vesanoid†; ***Venez.***: Betarretin; Retacnyl; Tretinax; Vesanoid.

Multi-ingredient Preparations. *Arg.*: Acneout; Hidrosam T; Melasmax; Neoblanc; Puraloe; Stievamycin; Tratacne; Tri-Luma; Trimegtante; Verrugard; ***Austria***: Keratosis forte; ***Braz.***: Hormoskin; Suavicid; Tri-Luma; Triderm; Vitacid Acne; Vitacid Plus; ***Canad.***: Biacna; Solage; Stievamycin; ***Chile***: Dermodan Plus; Erylik; Stievamycin; Taripel; Tri-Luma; ***China***: Puqing (芙晴); Jin Niu Er (金纽尔); *Cz.*: Aknemycin Plus; ***Fin.***: Wicaran; ***Fr.***: Erylik; ***Ger.***: Aknemycin Plus; Balisa VAS; Carbamid + VAS; Pigmanorm; Ureotop + VAS; ***Hong Kong***: Aknemycin Plus; Erylik; Tri-Luma; ***Hung.***: Verra-med; ***India***: A-Ret HC; Acsolve-C; Acsolve-H; Aknemycin Plus; Depig-TM; Eveglow; M-Lite; Melacare; Melacut; Melalite Plus; Melalite-XL; Melalong; Melanorm-HC; Multi-HTM; ***Indon.***: Erymed Plus; Medi-Klin TR; Refaquin; ***Israel***: Aknemycin Plus; ***Malaysia***: Aknemycin Plus; Efasol; Tri-Luma; ***Mex.***: Stievamycin; Tri-Luma; ***Philipp.***: Tri-Luma; ***Pol.***: Aknemycin Plus; ***Singapore***: Aknemycin Plus; Tri-Luma; ***Spain***: Loderm Retinoico†; ***Switz.***: Carbamide + VAS; Pigmanorm; Sebo-Psor; Verra-med; ***Thai.***: Tri-Luma; ***Turk.***: Eritretin; ***UK***: Aknemycin Plus; ***USA***: Solage†; Tri-Luma; Ziana; ***Venez.***: Tri-Luma.

Pharmacopoeial Preparations

BP 2014: Tretinoin Gel; Tretinoin Solution;
USP 36: Tretinoin Cream; Tretinoin Gel; Tretinoin Topical Solution.

Trichloroacetic Acid

Acide Trichloracétique; Acidum trichloraceticum; Acidum Trichloroaceticum; Kwas trichlorooctowy; Kyselina trichloroctová; Trichloracetic Acid; Trichloracto rūgštis; Trichloressigsäure; Tricloroacético, ácido; Trikloorietikkahappo; Triklorättiksyra; Triklórecetsav; Трихлоруксусная Кислота.

$C_2HCl_3O_2$=163.4
CAS — 76-03-9.
UNII — 5V2JDO056X.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Trichloroacetic Acid). A very deliquescent white or almost white crystalline mass or colourless crystals. Very soluble in water, in alcohol, and in dichloromethane. Store in airtight containers.

Uses and Administration

Trichloroacetic acid is caustic and astringent. When used as an escharotic for warts it is applied as a strong solution; a range of concentrations have been used including 50% and 80%. The surrounding areas of skin should be protected. Trichloroacetic acid has also been used for the removal of tattoos and in cosmetic surgery for chemical peeling of the skin.

Tattoo removal. References to the use of trichloroacetic acid in the removal of tattoos.

1. Hall-Smith P, Bennett J. Tattoos: a lasting regret. *BMJ* 1991; 303: 397.

Warts. References to the use of trichloroacetic acid in the treatment of genital warts (p. 1689.3).

1. Godley MJ, *et al.* Cryotherapy compared with trichloroacetic acid in treating genital warts. *Genitourin Med* 1987; 63: 390–2.
2. Davis AJ, Emans SJ. Human papilloma virus infection in the pediatric and adolescent patient. *J Pediatr* 1989; 115: 1–9.
3. Boothby RA, *et al.* Single application treatment of human papillomavirus infection of the cervix and vagina with trichloroacetic acid: a randomized trial. *Obstet Gynecol* 1990; 76: 278–80.
4. Abdullah AN, *et al.* Treatment of external genital warts comparing cryotherapy (liquid nitrogen) and trichloroacetic acid. *Sex Transm Dis* 1993; 20: 344–5.

Adverse Effects and Treatment

As for Hydrochloric Acid, p. 2529.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Wartner Stift; *Ital.*: CL tre; Verrupor; *USA*: Tri-Chlor.

Multi-ingredient Preparations. *Turk.*: IL-33.

Trioxysalen *(rINN)*

NSC-71047; Trioksisaleeni; Trioxisalen; Trioxisaleno; Trioxsalen (USAN); Trioxysalène; Trioxysalenum; Триоксизален; 4,5',8-Trimethylpsoralen.

2,5,9-Trimethyl-7*H*-furo[3,2-*g*][1]benzopyran-7-one.
$C_{14}H_{12}O_3$=228.2
CAS — 3902-71-4.
ATC — D05AD01; D05BA01.
ATC Vet — QD05AD01; QD05BA01.
UNII — Y6UYBQV51T.

Pharmacopoeias. In *US.*

USP 36: (Trioxsalen). A white to off-white or greyish, odourless, crystalline solid. Practically insoluble in water; soluble 1 in 1150 of alcohol, 1 in 84 of chloroform, 1 in 43 of dichloromethane, and 1 in 100 of methyl isobutyl ketone. Protect from light.

Profile

Trioxysalen, a psoralen, is a photosensitiser used similarly to methoxsalen in photochemotherapy or PUVA therapy (p. 1712.1). Trioxysalen may be used topically in the PUVA treatment of psoriasis. It has also been used orally in idiopathic vitiligo to enhance pigmentation or increase the tolerance to sunlight in selected patients.

References.

1. Snellman E, Rantanen T. Concentration-dependent phototoxicity in trimethylpsoralen bath psoralen ultraviolet A. *Br J Dermatol* 2001; 144: 490–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fin.*: Tripsor†; *Gr.*: Trisoralen; *India*: Dermtone; Dsorolen.

Pharmacopoeial Preparations

USP 36: Trioxsalen Tablets.

Urea ⊗

Carbamida; Carbamide; E927b; Harnstoff; Karbamid; Karbamidi; Mocznik; Močovina; Üre; Urée; Urea; Ureum; Ureja; Карбамид; Мочевина.

Carbonic acid diamide.
$NH_2CO.NH_2$=60.06
CAS — 57-13-6.
ATC — B05BC02; D02AE01.
ATC Vet — QB05BC02; QD02AE01.
UNII — 8W8T17847W.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*. *US* also includes Urea C13.

Ph. Eur. 8: (Urea). Transparent, slightly hygroscopic, crystals or a white or almost white, crystalline powder. Very soluble in water; soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

USP 36: (Urea). Colourless or white, practically odourless, prismatic crystals, or white crystalline powder or pellets. May gradually develop a slight odour of ammonia on prolonged standing. Soluble 1 in 1.5 of water, 1 in 10 of alcohol, and 1 in 1 of boiling alcohol; practically insoluble in chloroform and in ether. Solutions are neutral to litmus. Store at a temperature of 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Incompatibility. Urea can cause haemolysis when mixed with blood and should never be added to whole blood for transfusion or given through the same set by which blood is being infused.

Uses and Administration

Urea promotes hydration and is mainly applied topically in the treatment of ichthyosis and hyperkeratotic skin disorders (p. 1685.1). Used intravenously it has osmotic diuretic properties similar to mannitol (p. 1427.3) and has been used in the treatment of acute increases in intracranial pressure (p. 1271.3), due to cerebral oedema, and to decrease intra-ocular pressure in acute glaucoma (p. 1999.1), but has been largely superseded by mannitol. Urea has also been given intra-amniotically for the termination of pregnancy (p. 2131.3).

When applied topically urea has hydrating and keratolytic properties. In the management of ichthyosis and other dry skin disorders it is applied in creams or lotions containing 5 to 25% urea; higher concentrations of 30% and 40% have also been used in severe cases. A preparation containing 40% may be used for nail destruction.

For the reduction of raised intracranial or intra-ocular pressure, urea is given intravenously, as an infusion of a 30% solution in glucose 5 or 10% or invert sugar 10%, at a rate not exceeding 4 mL/minute, in a dose of 0.5 to 1.5 g/kg to a maximum of 120 g daily. Doses used in children are based on the same regimen, but see also below. Rebound increases in intracranial and intra-ocular pressure may occur after about 12 hours.

Solutions of urea 40 to 50% have been given by intra-amniotic injection for the termination of pregnancy.

Urea labelled with carbon-13 (p. 2470.3) is used in the *in vivo* diagnosis of *Helicobacter pylori* infection (see Peptic Ulcer Disease, p. 1813.2). The test involves collecting a breath sample before and after oral ingestion of a single dose of ^{13}C-urea. *H. pylori* produces urease which hydrolyses the urea to carbon dioxide and ammonia; therefore, an excess of carbon-13-labelled carbon dioxide in the sample, compared with a baseline sample, indicates infection. Doses of ^{13}C-urea include 50 mg, 75 mg, or 100 mg depending on the kit being used. Urea labelled with the radionuclide carbon-14 (p. 2223.2) is also used in a urea breath test for *H. pylori* detection.

Administration in children. For the reduction of raised intracranial or intra-ocular pressure in children, urea is given intravenously in dosage regimens similar to those used in adults (see above). However, for children under 2 years of age, a dose of 100 mg/kg may be adequate.

Breath test kits containing ^{13}C-urea for the diagnosis of *Helicobacter pylori* infection are available for children. However, the *BNFC* states that the appropriateness of testing in children has not been established, and that endoscopy with biopsy is more accurate than *in vivo* breath testing, which is frequently unreliable in children.

Syndrome of inappropriate ADH secretion. For mention of the use of oral urea in the syndrome of inappropriate ADH secretion, see p. 2351.2.

Adverse Effects and Precautions

As for Mannitol, p. 1428.3. Urea should also be used with caution in liver impairment as blood-ammonia concentrations can rise, and should be avoided in liver failure.

Urea is reported to be more irritant than mannitol, and intravenous use may cause venous thrombosis or phlebitis at the site of injection; extravasation may cause sloughing or necrosis. Only large veins should be used for infusion, and urea should not be infused into veins of the lower limbs of elderly patients. Extreme care is essential to prevent accidental extravasation of urea infusions.

Rapid intravenous injection of solutions of urea can cause haemolysis; the risk is reduced by using glucose or invert sugar solutions as diluent. Urea should not be mixed with whole blood.

Topical applications may be irritant to sensitive skin.

Infants and neonates. High plasma-urea concentrations have been reported[1,2] in neonates after topical application of emollient creams containing urea. Since there was no evidence of dehydration[2,3] absorption of urea through the skin was the likely cause. Raised plasma-urea concentrations have been reported[4] in infants with erythematous skin conditions who had not been treated with urea cream and this was attributed to dehydration due to increased insensible water loss through the damaged skin.

1. Beverley DW, Wheeler D. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1986; 61: 696–8.
2. Oudesluys-Murphy AM, van Leeuwen M. High plasma urea concentrations in collodion babies. *Arch Dis Child* 1987; 62: 212.
3. Beverley DW, Wheeler D. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; 61: 1245–6.
4. Garty BZ. High plasma urea concentration in babies with lamellar ichthyosis. *Arch Dis Child* 1986; 61: 1245.

Pregnancy. There have been reports of women suffering coagulopathy associated with urea treatment given for termination of pregnancy.[1,2]

1. Grundy MFB, Craven ER. Consumption coagulopathy after intra-amniotic urea. *BMJ* 1976; 2: 677–8.
2. Burkman RT, *et al.* Coagulopathy with midtrimester induced abortion: association with hyperosmolar urea administration. *Am J Obstet Gynecol* 1977; 127: 533–6.

Pharmacokinetics

Urea is fairly rapidly absorbed from the gastrointestinal tract but causes gastrointestinal irritation. Urea is distributed into extracellular and intracellular fluids including lymph, bile, CSF, and blood. It is reported to cross the placenta, and penetrate the eye. It is excreted unchanged in the urine.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hidroplus; Keratopic; Locilherp; Nutralcon; Ureadin; Urecrem Hidro; Uremol; Xerobase; *Austral.*: Aquacare; Hamilton Skin Therapy; Nutraplus; Urecare†; Urederm; *Braz.*: Emoderm; Hidrapel Plus; Nutraplus; Ureadin; Ureativ; Urepel; *Canad.*: Dermaflex HC; Dermaflex†; Simply Botanical Sensations Healing Hands; Urederm†; Uree†; Uremol; Urisec; *Chile*: Ayr con urea; Ayr-5; Eucerin; Hyderm; Iso-Urea; Uramol; Ureadin 10 and 20; *Cz.*: Elacutan†; Excipial U; Linola Urea†; *Fin.*: Canoderm; Fenuril; *Fr.*: Anti-Dessechement†; Keratosane; Nutraplus†; Onypso; Sedagel†; *Ger.*: Ballsa; Basodexan; Elacutan; Hyanit N†; Linola Urea; Nubral; Onychomal; Onypso; Onyster; Ureotop; *Hong Kong*: Carmol; Carudermа; Buderm; Urecare; Urederm†; Ureson†; *Hung.*: Linola Urea; *Indon.*: Calmuderm†; Carmed; Moisderm; Soft U Derm; Urederm†; *Irl.*: Aquadrate; Nutraplus; *Ital.*: Dermal Care; *Jpn*: Keratinamin; *Malaysia*: Balneum Intensiv; Buderm†; Nutraplus; UO; *Mex.*: Derma-Keri; Dermoplast; Karmosan; Nutraplus; Uramol; *Norw.*: Canoderm; *NZ*: Aquacare†; Nutraplus; *Philipp.*: Nutraplus; *Port.*: Ureadin 5, 10, 20, 30, and 40; *S.Afr.*: Eulactol; Nutraplus; *Singapore*: Aqurea; Excipial U; Nutraplus; UO; Urecare†; *Swed.*: Calmuril; Canoderm; Caress; Fenuril; Karbasal; Monilen†; *Switz.*: Carbaderm; Carbamide Creme Nouvelle Formule; Carbamide Emulsion; Cremolan; Eucerin peau seche; Excipial U; Linola Uree; Nutraplus; Onypso; Onyster; *Thai.*: DiabeDerm; Nutraplus; U10; U20; UO; *Turk.*: Excipial; Nutraplus; Urederm; *UK*: Aquadrate; Dermatonics Heel Balm; Hydromol Intensive; Nutraplus; *Ukr.*: Carboderm (Карбодерм); Excipial U (Эксципиал М); *USA*: Aluvea; Aquacare; BP; Carmol; Dermal Therapy; Flexitol Heel Balm; Gormel; Hydro; Kerafoam; Keralac†; Kerol†; Lanaphilic; Nutraplus; RE-U40†; Rinnovi†; TL; Ultra Mide; Umecta; Uramaxin; Ureacin; Urealac†; Ureaphil†; Utopic; Vanamide; *Venez.*: Aquaphar; Dermisol; Uricrim.

Multi-ingredient Preparations. *Arg.*: Acilac; Akerat; Aloebel; Cremsor N; Hairplus; Hidrolac; Lactiderm; Lactocrem; Lactoplus; Masivol Urea; Novofarma; Oxidermos; Sadeltan P; Turgent Colageno; Turgent Emulsion; Ureadin Facial; Urecrem; Vansame; *Austral.*: Aussie Tan Skin Moisturiser†; Calmuril; Dermadrate; FootSmart; Hamilton Skin Active Urederm Cream; Psor-Asist; Psor-Asist; *Austria*: Calmuril; Canesten Bifonazol comp; Keratosis forte; Keratosis; Mirfulan; Optiderm; *Braz.*: Donnagel; Oticerim; Tricolpex; Tricomax; Vagi Biotic; Vagi-Sulfa; *Canad.*: Dr Scholl's Cracked Heel Relief†; Flexitol Heel Balm†; Hydrophil; Kerasal; Uremol-HC; *Chile*: Akerat; Ureadin 30; Ureadin Facial Antiarrugas; Ureadin Facial; Ureadin Forte; Ureadin Pediatrics; Ureadin Rx DB; Ureadin Rx PS; Ureadin Rx RD; Urealeti; *China*: Compound Indometacin (复方吲哚美辛); Gan Bi Mei (干披美); Runbao (润葆); *Cz.*: Betacorton U†; Kerasal; Mycospor Sada na Nehty; *Fin.*: Calmuril; Wicaran; Wicarba; *Fr.*: Akerat; Amycor Onychoset; Day Peel†; Night Peel†; PSO†; Topicrem†; Totephan†; *Ger.*: Ballsa VAS; Brand- u. Wundgel-Medice; Canesten Extra Nagelset; Carbamid + VAS; Fungidexan; Hydrodexan; MedEctoin; Mirfulan; Optiderm; Psoradexan; Remederm; Ureotop + VAS; *Gr.*: Lyoderm; Urecortin; *Hong Kong*: Dermadrate; *Hung.*: Canespro; Reseptyl-Urea; Squa-med; *India*: Basic; Clomic-S; Copriderm; Cotaryl; Cutivate-MF; Dew Derm; Diafoot; Dibi; Diprosis; Diprovate-MF; Epicort-MK; Foot Care; Gowet; Heelcare; Lobate-S; Moisturex; *Indon.*: Foothy; *Irl.*: Alphaderm; Calmurid HC; Calmurid; Cymex; Itch Relief; *Israel*: Agispor Onychoset; Calmurid†; Derma-Care†; Keratospor; U-Lactin Foot Cream; U-Lactin; *Ital.*: Eudermico; Ipso Urea; Keraflex; Optiderm; Perfluxi Cremagel; Synchrobase Duo; Verunec; Xerial; *Malaysia*: Balneum Intensiv Plus; Ucort; *Mex.*: Lowila; Mycospor Onicoset; Suavene; Urader Lactato; Ureaderm Lactato; *Neth.*: Calmurid HC; Calmurid; *NZ*: Dermadrate†; *Philipp.*: Remederm†; *Pol.*: Hasceral; Keratolit†; Mycospor Onychoset; Optiderm†; SolcoKerasal; Sterovag†; *Port.*: Calmurid; Creme Laser Hidrante†; U Lactin†; Ureadin 10 Plus; Ureadin Facial; Ureadin Forte; Ureadin Manos; Ureadin; *Rus.*: Kleore (Клеоре); Mycospor (Микоспор); *S.Afr.*: Covancaine; Mycospor Onycho-set†; *Singapore*: Balneum Intensiv Plus; Balneum Intensiv; Dermadrate; Topicrem; U-Lactin†; Ucort; *Spain*: Cortisdin Urea†; Kanapomada†; Mycospor Onicoset; Nasopomada†; *Swed.*: Penuril-Hydrokortison; *Switz.*: Acne Gel; Betacortone; Calmurid; Carbamide + VAS; Kerasal; Klyx Magnum†; Optiderm; Pruri-med Lipolotion; Sebo-Psor; Turexan Capilla†; Undex; *Thai.*: Gynestin; *Turk.*: Betacorton; Kerasal; Mycospor; Ureacort; *UK*: Alphaderm; Antipeol; Balneum Plus; Balneum; Calmurid HC; Calmurid; Cymex; E45 Itch Relief; Flexitol Heel Balm; Hydromol HC Intensive; St James Balm; Vesagex Heelbalm; *Ukr.*: Canespor Set (Канеспор Набор); Kerasal (Кераса); Mycospor Kit (Микоспор Набор)†; Prednicarb (Предникарб); *USA*: Accuzyme†; AllanEnzyme†; Allanfil-lEnzyme†; Amino-Cerv; Carb-O-Lac HP; Duraflex Comfort; Gladase-C†; Gladase†; Gold Bond Foot Pain Relieving; Hydrocerin Plus; Kerasal Ultra; Keratol HC; Kovia†; Latrix XM; Panafil-White†; Panafil†; Rosula NS†; Rosula†; Salvax Duo; Toetal Fresh; Ultralytic 2; Ziox†; Zoderm; *Venez.*: Akerat; Caduril; Hidribet 5/5; Hidribet; Mycospor Onicoset; Pantonic; Pelset Plus; Ureaderm Lactato.

Homoeopathic Preparations. *Ger.*: Girheulit HM†.

Pharmacopoeial Preparations
BP 2014: Urea Cream;
USP 36: Urea for Injection.

Ustekinumab *(BAN, USAN, rINN)*

CNTO-1275; Ustékinumab; Ustekinumabum; Устекинумаб. Immunoglobulin G1, anti-(human interleukin-12 subunit beta (IL-12B, CLMF p40, NKSF2))(human monoclonal CNTO 1275 γ1-chain), disulfide with human monoclonal CNTO 1275 κ-chain, dimer.

CAS — 815610-63-0.
ATC — L04AC05.
ATC Vet — QL04AC05.
UNII — FU77B4U5Z0.

Uses and Administration

Ustekinumab is a human monoclonal antibody that binds to interleukins 12 and 23, and is used for the treatment of moderate to severe plaque psoriasis (p. 1688.1). It is given to patients aged 18 years and over who have not responded to, or are unable to take, other systemic therapies. Ustekinumab is given by subcutaneous injection, but it should not be injected into areas that show psoriasis. An initial dose of 45 mg is repeated after 4 weeks, then every 12 weeks thereafter. A dose of 90 mg should be used for patients weighing more than 100 kg. Treatment should be stopped if there is no response after 28 weeks of therapy.

Ustekinumab is under investigation in the treatment of psoriatic arthritis, Crohn's disease, and multiple sclerosis.

References.

1. Krueger GG, *et al.* A human interleukin-12/23 monoclonal antibody for the treatment of psoriasis. *N Engl J Med* 2007; 356: 580–92.
2. Leonardi CL, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008; 371: 1665–74. Correction. *ibid.*: 1838.
3. Papp KA, *et al.* Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet* 2008; 371: 1675–84.
4. Gottlieb A, *et al.* Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; 373: 633–40. Correction. *ibid.* 2010; 376: 1542.
5. Griffiths CE, *et al.* ACCEPT Study Group. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; 362: 118–28.
6. Croxtall JD. Ustekinumab: a review of its use in the management of moderate to severe plaque psoriasis. *Drugs* 2011; 71: 1733–53.

Adverse Effects and Precautions

Upper respiratory-tract infections and nasopharyngitis are very common adverse effects of ustekinumab treatmen . Other effects that occur commonly include pharyngolaryngeal pain, nasal congestion, cellulitis, diarrhoea, back pain, myalgia, pruritus, dizziness, headache, fatigue, and depression. Injection site reactions can occur, and hypersensitivity reactions such as rash and urticaria have been reported. Reduced efficacy has been found in patients who have developed antibodies to ustekinumab.

As a result of immunosuppression, patients given ustekinumab are at increased risk of infection. It should not be given to patients with a serious infection and should be used with care in those with chronic infection or a history of recurring infection. Serious bacterial, viral, and fungal infections have occurred. Live or live-attenuated vaccines should not be given during ustekinumab treatment because of the risk of infection. It should be withheld from at least 15 weeks before until 2 weeks after vaccination. Immunosuppression caused by ustekinumab might also increase the risk of developing malignancies, so it should be used with care in patients with a history of malignancy and those who develop malignancy during ustekinumab therapy.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies ustekinumab as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Interactions

For a warning concerning the use of live vaccines in patients receiving ustekinumab, see Adverse Effects and Precautions, above.

Pharmacokinetics

Peak serum concentrations of ustekinumab occur about 8.5 days after a subcutaneous dose, and its bioavailability is about 57%. Its elimination half-life is about 3 weeks, ranging from 15 to 32 days. Ustekinumab is cleared more rapidly in heavier patients (e.g. more than 100 kg). Pharmacokinetic analysis also suggests higher clearance in patients who test positive for antibodies to ustekinumab.

References.

1. Zhu Y, *et al.* Population pharmacokinetic modeling of ustekinumab, a human monoclonal antibody targeting IL-12/23p40, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol* 2009; 49: 162–75.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Stelara; *Austral.*: Stelara; *Austria*: Stelara; *Belg.*: Stelara; *Braz.*: Stelara; *Canad.*: Stelara; *Cz.*: Stelara; *Denm.*: Stelara; *Fr.*: Stelara; *Ger.*: Stelara; *Gr.*: Stelara; *Hong Kong*: Stelara; *Hung.*: Stelara; *Irl.*: Stelara; *Israel*: Stelara; *Jpn*: Stelara; *Neth.*: Stelara; *Norw.*: Stelara; *Pol.*: Stelara; *Port.*: Stelara; *Rus.*: Stelara (Стелара); *Singapore*: Stelara; *Spain*: Stelara; *Swed.*: Stelara; *Switz.*: Stelara; *Thai.*: Stelara; *UK*: Stelara; *USA*: Stelara.

Zinc Carbonate *(USAN)*

Zinc, carbonato de; Карбонат Цинка; Углекислый Цинк.

$ZnCO_3$=125.4

CAS — 3486-35-9.
UNII — EQR32Y7H0M.

Basic Zinc Carbonate

Zinc, carbonato básico de; Основный Карбонат Цинка; Основный Углекислый Цинк.

NOTE. The names zinc carbonate, hydrated zinc carbonate, zinc subcarbonate, and zinc carbonate hydroxide have all been applied to basic zinc carbonate of varying composition occurring naturally or produced by the reaction of a soluble zinc salt with sodium carbonate.

Pharmacopoeias. In *US.*

USP 36: (Zinc Carbonate). It corresponds to $3Zn(OH)_2.2ZnCO_3$ containing the equivalent of not less than 70% ZnO. Store in airtight containers.

Profile

Zinc carbonate is mildly astringent and protective to the skin and is used topically, mainly in the form of calamine (p. 1697.2), in a variety of skin conditions. In the USA the

name calamine is used for zinc oxide (rather than zinc carbonate) with a small proportion of ferric oxide.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ukr.*: Bezornil (Безорнил).

Zinc Oxide

Flowers of Zinc; Blanc de Zinc; Blanco de zinc; Cinko oksidas; Çinko Oksit; Cink-oxid; Cynku tlenek; Flores de zinc; Oxid zinečnatý; Sinkkioksidi; Zinc, óxido de; Zinc, oxyde de; Zinci oxidum; Zinci Oxydum; Zincum Oxydatum; Zinkoxid; Оксид Цинка; Цинк Оксид.

ZnO=81.38

CAS — 1314-13-2.

UNII — SOI2LOH54Z.

NOTE. 'Zinc White' is a commercial form of zinc oxide used as a pigment.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

US also includes a neutral zinc oxide.

Ph. Eur. 8: (Zinc Oxide). A white or faintly yellowish-white, soft, amorphous powder, free from gritty particles. Practically insoluble in water and in alcohol; it dissolves in dilute mineral acids.

USP 36: (Zinc Oxide). A white or yellowish-white, odourless, amorphous, very fine powder, free from grittiness. It gradually absorbs carbon dioxide from air. Insoluble in water and in alcohol; soluble in dilute acids.

USP 36: (Zinc Oxide, Neutral). It is for use in sunscreen preparations only.

Incompatibility. Black discoloration has been reported when zinc oxide and glycerol are in contact in the presence of light.

Profile

Zinc oxide is mildly astringent and is used topically as a soothing and protective application in eczema and slight excoriations, in wounds, and for haemorrhoids. It is also used with coal tar (p. 1723.3) or ichthammol (p. 1705.3) in the treatment of eczema. Zinc oxide reflects ultraviolet radiation and is used as a physical sunscreen (see p. 1681.3).

In the USA the name calamine is used for zinc oxide with a small proportion of ferric oxide.

Zinc oxide is used as the basis for the production of many dental cements. Mixed with phosphoric acid it forms a hard material composed largely of zinc phosphate; mixed with clove oil or eugenol, it is used as temporary dental filling.

For further details of zinc and its salts, see p. 2126.1.

Complications of dental use. Solitary aspergillosis of the maxillary sinus in 29 of 30 patients was associated with zinc oxide from overfilled teeth.[1] Treatment consisted of removal of the fungal ball containing the zinc oxide; no antifungal treatment was necessary. Zinc oxide has been shown to accelerate the growth of *Aspergillus fumigatus*. Further cases have been reported, and adjunctive systemic antifungal treatment has been used.[2]

1. Beck-Mannagetta J, *et al.* Solitary aspergillosis of maxillary sinus, a complication of dental treatment. *Lancet* 1983; ii: 1260.
2. Martins WD, Ribeiro Rosa EA. Aspergillosis of the maxillary sinus: review and case report. *Scand J Infect Dis* 2004; 36: 758–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Cutidermin Bebe Crema Protectora†; Dermic Sinamida D; Zincoxid; ***Austral.***: Clear Zinke; Curash Anti-Rash; Gelocast; Prickly Heat Powder; Rectogesic; Steripaste; Sudocrem; UV Triplegard Natural; Viscopaste; Zincaband; Zinke; Zipzoc; ***Braz.***: Bebex Previne; Dermodex Prevent; ***Canad.***: Aveeno Diaper Rash†; Diaper Rash; Diaper-Care†; Johnson's Diaper Rash†; Sunblock†; Viscopaste PB7; Woodward's Diaper Rash; Zinaderm; Zincoderm†; Zincofax; Zipzoc; ***Chile***: Desitin Creamy; Nenegloss Z; Unitone 4; ***Denm.***: Zipzoc; ***Fin.***: Zipzoc; ***Fr.***: Babygella; Oxyplastine; Veinopress A3 and A4; ***Ger.***: Guta; Pantederm N†; Retterspitz Heilsalbe ST; Zinksalbe Lichtenstein; ***Hong Kong***: Zinoxid†; ***Irl.***: Steripaste; Viscopaste; Zipzoc; ***Israel***: Dyprotex; Lotio Zinci; Zinc Lotion; ***Ital.***: Ceroxmed Tex; Cincream; Delicate Skin Pasta; Gelocast; Gelostretch; Milsana; Oz; Scherilan Crema; Sicura3 Fisionorm; Tayderm; Tendigrip; Triderm Crema; Triderm Zeta; Varicex; Viscopaste PB7; Zinco Acqua; Zincoderm; Zincotape; ***Mex.***: Pasta de Lassar; Saniderm; ***Neth.***: Daro Zinkzalf; Zinkolie; Zinkzalf; Zipzoc†; ***Philipp.***: Curash; Desitin; Rashfree; Spectraban 19; ***Port.***: Lassadermil; Zincoderma; Zipzoc; ***Rus.***: Cindol (Циндол); Desitin (Деситин); ***S.Afr.***: Clocktower†; Johnson's Baby Nappy Cream; Vernleigh Baby Cream; Viscopaste PB7†; ***Singapore***: Desitin; Nu-Derm Physical UV Block; ***Spain***: Anticongestiva; ***Swed.***: Zipzoc Salvstrumpa; ***Switz.***: Oxyplastine; Zin-Cream; ***Thai.***: Cabana; Nappy-Hippo; Spectraban†; ***UAE***: Proskin; ***UK***: Steripaste; Viscopaste PB7; Zincaband; Zipzoc; ***Ukr.***: Desitin (Деситин); ***USA***: Balmex Diaper Rash; Bensons Bottom; Borofax; Delazinc; Diaparene Diaper Rash; Dr Smiths; Triple Paste; ***Venez.***: Cicalfate; Lanol-Zinc; Oxyphar.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. ***Canad.***: Homeo-S-Asp; Sportenine; ***Fr.***: Sportenine; ***Neth.***: Sportenine†.

Pharmacopoeial Preparations

BP 2014: Aqueous Calamine Cream; Calamine and Coal Tar Ointment; Calamine Lotion; Coal Tar and Zinc Ointment; Coal Tar Paste; Compound Aluminium Paste; Compound Zinc Paste; Dithranol Paste; Hexachlorophene Dusting Powder; Zinc and Castor Oil Ointment; Zinc and Coal Tar Paste; Zinc and Ichthammol Cream; Zinc and Salicylic Acid Paste; Zinc Cream; Zinc Ointment;

USP 36: Calamine Topical Suspension; Coal Tar Ointment; Compound Resorcinol Ointment; Zinc Oxide and Salicylic Acid Paste; Zinc Oxide Ointment; Zinc Oxide Paste.

Zinc Phenolsulfonate

4-Hidroxibencenosulfonato de zinc; Phenozin; Zinc, fenosulfonato de; Zinc 4-hydroxybenzenesulphonate; Zinc Phenolsulphonate; Сульфофенолят Цинка; Фенолсульфонат Цинка.

Zinc *p*-hydroxybenzenesulphonate

$C_{12}H_{10}O_8S_2Zn$=411.7

CAS — 127-82-2.

UNII — 4O71YT5YB5.

Profile

Zinc phenolsulfonate has astringent properties and has been used in multi-ingredient preparations applied topically for the treatment of a variety of disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. ***Arg.***: Gineseptina; ***Braz.***: Lerin; Neo Quimica Colirio†; Visazul; ***Canad.***: Sil Trax Plus†; ***Ital.***: Antisettico Astringente Sedativo; Oftalmil; ***USA***: BFI.

Disinfectants and Preservatives

This chapter describes those antimicrobial agents that are used for chemical methods of disinfection, antisepsis, preservation, and sterilisation. The collective term biocides has been used to describe such agents. There is some overlap between these procedures and some agents may be used as both disinfectants and preservatives. Iodine (p. 2336.3), not in this chapter, is also used for its disinfectant properties.

Definition of terms. There is often confusion between the terms disinfectant and antiseptic.

- The term **disinfectant** is applied to a chemical agent that destroys or inhibits the growth of pathogenic micro-organisms in the non-sporing or vegetative state; disinfectants do not necessarily kill all micro-organisms, but reduce them to a level that is harmful neither to health nor the quality of perishable goods. The term is applicable to agents used to treat inanimate objects and materials and may also be applied to agents used to treat the skin and other body membranes and cavities
- An **antiseptic** is a disinfectant that is used on skin and other living tissues thereby limiting or preventing infection
- **Sterilisation** is the total removal or destruction of all living micro-organisms; a few disinfectants (such as ethylene oxide) are capable of producing sterility under suitable conditions but, in general, sterility is produced by heat or radiation methods, with filtration being used for some heat-labile materials. Sterilisation by heating with a bactericide is no longer a recommended practice
- A **preservative** is one of several chemical agents that are included in preparations to prevent deterioration from oxidation (**antoxidants**) or to kill or inhibit the growth of micro-organisms inadvertently introduced during manufacture or use (**antimicrobial preservatives**).

Use of disinfectants. Disinfectants are used in hospitals, industrial establishments, public buildings, on farms, and in the home for control and prevention of infection.

The choice of disinfectant depends on the purpose for which it is used and the likely contaminating organisms. In addition to vegetative bacteria, many common disinfectants could be expected to kill some fungi and lipid-containing viruses. Gram-negative bacteria, mycobacteria, and bacterial spores are generally more resistant to disinfectants, and some disinfectants are less effective against non-lipid enveloped viruses, for example the enteroviruses including polio and coxsackie. Prions are generally resistant to many disinfectants (see Disinfection in Creutzfeldt-Jakob Disease, below). Other factors affecting the efficacy of disinfectants include the contact time, concentration of the disinfectant, the pH of the system, the number and accessibility of the contaminating micro-organisms, and the presence of interfering substances including lipids, organic matter, rubber, and plastics. Aqueous solutions of disinfectants, particularly quaternary ammonium compounds (such as benzalkonium chloride and cetrimide), chlorhexidine, and phenols, may be susceptible to contamination with micro-organisms. To reduce this risk many preparations are provided for clinical use in a sterile form for single use.

Use of preservatives. Antimicrobial preservatives are used in sterile preparations such as eye drops and multidose injections to maintain sterility during use. They may also be added to aqueous injections that cannot be sterilised in their final containers and have to be prepared using aseptic precautions, unless the volume to be injected as a single dose exceeds 15 mL. Antimicrobial preservatives are also used in cosmetics, foods, and non-sterile pharmaceutical products such as oral liquids and creams to prevent microbial spoilage. They should not be used indiscriminately. Preparations that should *not* contain preservatives include those for injection into the CSF, eye, or heart. Generally, the antimicrobial preservatives that may be added to foods, animal feeding stuffs, and cosmetics are controlled.

Preservatives used as antoxidants may be classified in 3 groups:

- ***true antoxidants***, or anti-oxygens, which probably inhibit oxidation by reacting with free radicals blocking the chain reaction. Examples are the alkyl gallates, butylated hydroxyanisole, butylated hydroxytoluene, nordihydroguaiaretic acid, and the tocopherols (see Vitamin E Substances, p. 2119.1)
- ***reducing agents***, which are substances having a lower redox potential than the drug or adjuvants that they are intended to protect and are therefore more readily oxidised. Reducing agents may act also by reacting with free radicals. Examples are ascorbic acid (p. 2110.3) and the potassium and sodium salts of sulfurous acid (see Sulfites and Sulfur Dioxide)
- ***antoxidant synergists***, which usually have little antoxidant effect themselves but probably enhance the action of antoxidants in the first group by reacting with heavy-metal ions which catalyse oxidation. Examples of synergists are citric acid (p. 2480.3), edetic acid and its salts (p. 1550.3), lecithin (p. 2542.2), and tartaric acid (p. 2626.1)

General references and guidelines for the use of disinfectants.

1. DoH. Standard principles for preventing hospital-acquired infections. *J Hosp Infect* 2001; 47 (suppl): S21–S37. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005417?IdcService=GET_FILE&dID=14080&Rendition=Web (accessed 27/08/08)
2. Block SS, ed. *Disinfection, sterilization, and preservation*. 5th ed. Philadelphia: Lippincott Williams and Wilkins, 2001.
3. Ayliffe GAJ, English MP. *Hospital infection: from Miasmas to MRSA*. Cambridge: Cambridge University Press,2003.
4. Fraise AP, *et al.*, eds. *Russel, Hugo and Ayliffe's principles and practice of disinfection, preservation, and sterilization*. 4th ed. Oxford: Blackwell Science, 2005.
5. Rutala WA, Weber DJ. Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for disinfection and sterilization in healthcare facilities, 2008. Available at: http://www.cdc.gov/hicpac/pdf/guidelines/Disinfection_Nov_2008.pdf (accessed 01/03/10)

Contact lens care

Wearers of contact lenses are at increased risk of corneal infections. Factors that predispose the cornea to infection include surface abrasions that may occur during normal wear, extended wear of soft (hydrogel) lenses, accidental trauma during insertion of a lens, and anoxia. In addition, the lens may provide a medium for introducing pathogens into the eye, especially if handling, cleaning, and disinfecting procedures are not followed. The most common pathogens are bacteria, in particular *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Staph. epidermidis*, and *Streptococcus pneumoniae*. Fungi rarely cause lens-related keratitis, although contamination of soft lenses has been reported. *Acanthamoeba* can cause rare but serious corneal infections (see Acanthamoeba Keratitis, p. 919.3) mainly associated with soft contact lens wear; these protozoa are resistant to some commonly used disinfection systems and can colonise lens storage cases.

Lens care systems for **rigid** (hard or gas-permeable) lenses typically entail cleansing and disinfection stages.

- Daily cleansing with solutions containing surfactants and sometimes mild abrasives can substantially reduce microbial contamination as well as removing organic material which can compromise the activity of the disinfection stage. Cleansing solutions frequently contain substances that are irritant to the eye and should be removed by rinsing and soaking the lens.
- Soaking solutions also maintain lens hydration, disinfect the lens, and prevent contamination during storage. Although not intended for use in the eye, soaking solutions should be non-irritant.
- Commonly used disinfectants include benzalkonium chloride and chlorhexidine. Thiomersal is also used but has been associated with a high incidence of hypersensitivity reactions.
- Wetting or rewetting solutions are used to improve the comfort of the lens and, since they are applied to the eye, must be non-irritant. They commonly contain hypromellose, hyetellose, polyvinyl alcohol, or povidone, although a simple sodium chloride 0.9% solution may be used.

Initially chemical disinfection for **soft** contact lenses required 4 steps; cleaning, rinsing, soaking in a disinfectant, and final rinsing. The introduction of multipurpose solutions containing small amounts of surfactant cleaner and disinfectant have reduced the number of steps required.

- Soft contact lenses contain a high proportion of water and are liable to absorb substances from solution. For this reason some disinfectants, notably benzalkonium chloride, are not suitable for inclusion in solutions for soft lenses. Soft lenses may be disinfected by heating in a suitable unit, usually in isotonic saline solution, but this can shorten the life of the lens by denaturing the polymer or causing deposits of denatured protein, minerals, or preservatives from the saline solution. Stabilised hydrogen peroxide is suitable for cold disinfection of soft lenses and is particularly useful for preventing *Acanthamoeba* infections. However, it is irritant to the cornea and must be neutralised before the lens is inserted into the eye. Other disinfectants for soft lenses may include chlorhexidine and polihexanide.
- Cleansers for soft lenses may contain surfactants or enzymes, such as papain or pancreatin, that remove protein deposits.
- Wetting solutions may be used similarly to rigid lenses

Reviews.

1. Rakow PL. Current contact lens care systems. *Ophthalmol Clin North Am* 2003; 16: 415–32.

Disinfection in Creutzfeldt-Jakob disease

Creutzfeldt-Jakob disease is a transmissible spongiform encephalopathy believed to be caused by infection of the nervous system with prions. The agent causing Creutzfeldt-Jakob disease (CJD) is resistant to many disinfection procedures including dry heat, ultraviolet irradiation, alcohols, ethylene oxide, eusol, formaldehyde, glutaral, hydrogen peroxide, iodine or iodophores, peracetic acid, phenolics, and propiolactone. Furthermore, aldehyde-type disinfectants have fixative proprieties and could anchor prion and other proteins to equipment and make them more difficult to remove by other means.[1] No sterilisation procedure can be guaranteed to be completely effective under all circumstances[1] and for disposable instruments and materials the safest method is to destroy them by incineration.[2] Neurosurgical and ophthalmic instruments should also be destroyed by incineration if used in patients with confirmed or suspected CJD. WHO[2] has developed guidelines for control of transmissible spongiform encephalopathies which include measures for the decontamination and cleaning of instruments and materials designed for re-use. They recommend that contaminated instruments and material should be kept moist between the time of use and decontamination and that one of the following methods of decontamination be used for heat-resistant instruments (listed in increasing order of severity):

- immerse in 1N sodium hydroxide and heat in a gravity displacement autoclave at 121 degrees for 30 minutes then clean, rinse in water, and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then transfer the instruments to water, heat in a gravity displacement autoclave at 121 degrees for 1 hour, then clean and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide or sodium hypochlorite (providing 20 000 ppm available chlorine) for 1 hour then remove and rinse in water, transfer to an open pan and heat in a gravity displacement (121 degrees) or porous load (134 degrees) autoclave for 1 hour, then clean and continue with routine sterilisation processes
- immerse in 1N sodium hydroxide and boil for 10 minutes at atmospheric pressure then clean, rinse in water, and continue with routine sterilisation processes
- immerse in sodium hypochlorite (providing 20 000 ppm available chlorine) (preferred) or 1N sodium hydroxide (alternative) at ambient temperature for 1 hour then clean, rinse in water, and continue with routine sterilisation processes
- autoclave at 134 degrees for 18 minutes

Heat sensitive instruments and surfaces should be decontaminated by flooding with 2N sodium hydroxide or undiluted sodium hypochlorite and left to stand for 1 hour, then mopped up and rinsed with water. If these agents cannot be tolerated then thorough cleaning with a diluted solution or other partially effective agent is advised.[2] In the UK, it is recommended[1] that if it is the intention to reuse an endoscope that has been employed in patients with suspected CJD or has been used for invasive procedures in those at risk of CJD (e.g. haemophiliacs), then the endoscope should be disinfected with a non-aldehyde single use disinfectant separately from other endoscopes and quarantined for use only in the same patient or in those with confirmed CJD. If the patient has confirmed CJD, then the quarantined endoscope can only be used in the same patient.

Recommendations for disinfection and sterilisation in CJD have also been published in the UK[3] and USA.[4,5]

1. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 01/03/10)
2. WHO. *WHO infection control guidelines for transmissible spongiform encephalopathies: report of a WHO consultation.* Geneva: WHO, 1999. Available at: http://whqlibdoc.who.int/hq/2000/WHO_CDS_CSR_APH_2000.3.pdf (accessed 15/03/06)
3. Advisory Committee on Dangerous Pathogens. Spongiform Encephalopathy Advisory Committee. *Transmissible spongiform encephalopathy agents: safe working and the prevention of infection.* London: DoH, 2003. Also available at: http://www.dh.gov.uk/ab/ACDP/TSEguidance/index.htm (accessed 01/04/10)
4. Rutala WA, Weber DJ. Creutzfeldt-Jakob disease: recommendations for disinfection and sterilization. *Clin Infect Dis* 2001; 32: 1348–56.
5. Rutala WA, Weber DJ. Society for Healthcare Epidemiology of America. Guideline for disinfection and sterilization of prion-contaminated medical instruments. *Infect Control Hosp Epidemiol* 2010; 31: 107–17. Also available at: http://www.journals.uchicago.edu/doi/pdf/10.1086/650197 (accessed 22/06/10)

Disinfection in dental practice

Dental patients and healthcare staff can be exposed to viruses and bacteria that are present in blood or colonise or infect the oral cavity and respiratory tract, such as CMV, hepatitis B and C viruses, herpes simplex virus types 1 and 2, HIV, *Mycobacterium tuberculosis*, staphylococci, and streptococci. For information on endocarditis prophylaxis with antibacterials, see p. 179.2. These organisms can be transmitted in dental settings through direct or indirect contact with blood, oral fluids, or other body matter; by indirect contact with contaminated objects (e.g. instruments, equipment, or environmental surfaces), or inhalation of airborne micro-organisms (which can remain suspended in the air for long periods).

Guidelines have been developed in the USA for preventing and controlling infectious diseases and managing personnel health and safety concerns related to infection control in dental settings.[1] **Hand hygiene** (see p. 1732.1) substantially reduces potential pathogens on the hands and is considered a critical measure for reducing the risk of transmitting organisms to patients and healthcare workers. For routine dental examinations and nonsurgical procedures, handwashing and hand antisepsis is achieved by using a plain or antimicrobial soap and water. If the hands are not visibly soiled, an alcohol-based hand rub may be used. Before surgical procedures an antimicrobial soap or alcohol hand rub with persistent activity should be used. This extended antimicrobial activity is needed to prevent the introduction of organisms, which can colonise the hands underneath gloves and enter the wound if gloves become punctured or torn.

Patient-care items such as dental instruments, devices, and equipment should be **cleaned** to remove debris as well as organic and inorganic contamination, before proceeding with disinfection and sterilisation. If manual cleaning cannot be done immediately, the instruments should be placed in a puncture-resistant container and soaked in a detergent, a disinfectant/detergent, or an enzymatic cleaner. Use of a liquid chemical sterilant/high-level disinfectant (e.g. glutaral) as a holding solution is not recommended.

Heat-tolerant dental instruments usually are **sterilised** by autoclaving, dry heat, or unsaturated chemical vapour. Three levels of **disinfection** are used for patient-care devices that do not require sterility:

- high (e.g. glutaral, hydrogen peroxide, hydrogen peroxide with peracetic acid, *o*-phthaldialdehyde, peracetic acid, and phenol with glutaral)
- intermediate (e.g. chlorine-containing products, iodophores, phenolics, and quaternary ammonium compounds with alcohol)
- low (e.g. quaternary ammonium compounds, some phenolics, and some iodophores)

Patient-care items are categorised as critical, semicritical, or noncritical, depending on the potential risk for infection associated with their intended use. Heat sterilisation is used for critical items (used to penetrate soft tissue or bone) also for semicritical items that touch mucous membranes or non-intact skin. Semicritical items that are heat-sensitive should be processed with high-level disinfection. Noncritical patient-care items, contacting only intact skin, just require cleaning, or if visibly soiled, cleaning followed by disinfection. When the item is visibly contaminated with blood or other potentially infectious material a disinfectant thought to be effective against tubercle bacilli (intermediate-level disinfectant) should be used.

Clinical contact surfaces can become contaminated from patient materials either by direct spray or spatter generated during dental procedures or by contact with dental healthcare workers' gloved hands. Two levels of disinfection, intermediate and low, are used for environmental surfaces. If protective barriers are not used, surfaces should be cleaned and disinfected between patients by using disinfectants effective against HIV or hepatitis B virus (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant) if the surface is visibly contaminated with blood or other potentially infectious material. General cleaning and disinfection are recommended for clinical contact surfaces, dental unit surfaces, and countertops at the end of daily work activities and are required if surfaces have become contaminated since their last cleaning. Spills of blood and other body fluids should be removed with absorbent material (e.g. disposable paper towels). Nonporous surfaces should be cleaned and then decontaminated with disinfectant effective against hepatitis B virus and HIV (low-level disinfectant) or a tuberculocidal disinfectant (intermediate-level disinfectant).

1. Kohn WG, *et al.* CDC guidelines for infection control in dental healthcare settings—2003. *MMWR* 2003; 52 (RR-17): 1–61. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5217.pdf (accessed 17/03/06)

Disinfection of endoscopes

Whenever possible, medical equipment that comes into intimate contact with the body should be heat sterilised, but some equipment, notably endoscopes, will not withstand high temperatures. Low-temperature steam and formaldehyde or ethylene oxide will achieve sterilisation, but may not be practical in a clinical setting. Satisfactory chemical disinfection of endoscopes and other heat-sensitive instruments relies on initial thorough cleansing of the instrument and choice of an appropriate high-level disinfectant which should be rapidly active against a wide range of pathogens including vegetative bacteria, bacterial spores, mycobacteria, and viruses. The disinfectant should not damage the instrument or discolour the optical components, and it should not leave a toxic residue. Instruments should be rinsed after disinfection with water and dried with forced air.[1-4]

Glutaral 2% is commonly used.[1,4] To achieve sterilisation, immersion in glutaral 2% for 3 hours is necessary, but high-level disinfection, achieved by immersion for 20 minutes, is usually considered adequate for most endoscopes.[1,3,5,6] Immersion for a minimum of 20 minutes is required for elimination of tubercle bacilli, but immersion for 4 minutes may be adequate for gastroscopes, except those for use on immunocompromised patients. For specific information relating to hepatitis and HIV viruses, see below.

A disadvantage of glutaral is that it is irritant and may cause sensitisation. In addition, longer contact times are needed to eliminate atypical mycobacteria and glutaral-resistant strains of *M. chelonae* have been isolated from endoscope disinfecting equipment.[4,7] In fact, mycobacteria in general are known to be extremely resistant to glutaral.[3] It should also be noted that in the UK it is recommended that units should move away from the use of aldehyde-based disinfectants because of their fixative properties, which in theory could anchor prion and other protein within endoscopes.[3] The use of aldehydes as the primary disinfectant should also be avoided in units serving groups at risk of CJD, such as haemophilia centres (see also Disinfection in Creutzfeldt-Jakob Disease, p. 1730.3). Alternative disinfectants include peracetic acid, chlorine dioxide, *o*-phthaldialdehyde, and superoxidised water (hypochlorous acid).[3,4,6] Other alternatives include peroxygen compounds, quaternary ammonium compounds, glucoprotamine, electrolysed acid water, succinic dialdehyde, and alcohol 70%.[1,4,6] However, peracetic acid and chlorine dioxide produce irritant fumes, peroxygen-containing compounds and quaternary ammonium compounds have questionable activity against mycobacteria and viruses, and alcohol has several practical limitations.[4,6]

1. Ayliffe GAJ, *et al. Chemical disinfection in hospitals.* 2nd ed. London: PHLS,1993.
2. Rutala WA, Weber DJ. Disinfection and sterilization in health care facilities: what clinicians need to know. *Clin Infect Dis* 2004; 39: 702–9.
3. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 26/02/10)
4. Beilenhoff U, *et al.* ESGE Guidelines Committee. European Society of Gastrointestinal Endoscopy. European Society of Gastroenterology and Endoscopy Nurses and Associates. ESGE-ESGENA guideline: cleaning and disinfection in gastrointestinal endoscopy. *Endoscopy* 2008; 40: 939–57. Also available at: http://www.esge.com/assets/downloads/pdfs/guidelines/2008_cleaning_and_disinfection.pdf (accessed 07/07/10)
5. American Society for Gastrointestinal Endoscopy. Multi-society guideline for reprocessing flexible gastrointestinal endoscopes. *Gastrointest Endosc* 2003; 58: 1–8. Also available at: http://www.asge.org/WorkArea/showcontent.aspx?id=3376 (accessed 27/08/08) Also published in: Nelson DB *et al.* Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 2003; 24: 532–7.
6. Alvarado CJ, *et al.* Association for Professionals in Infection Control. APIC guideline for infection prevention and control in flexible endoscopy. *Am J Infect Control* 2000; 28: 138–55.
7. Griffiths PA, *et al.* Glutaraldehyde-resistant Mycobacterium chelonae from endoscope washer disinfectors. *J Appl Microbiol* 1997; 82: 519–26.

Disinfection in hepatitis and HIV infection

Hepatitis viruses and HIV are susceptible to heat and the methods recommended for sterilisation of equipment in the UK[1] are conventional procedures using moist or dry heat. Heat-labile articles and surfaces may undergo chemical disinfection but only in the absence of a satisfactory alternative. Although various publications have claimed efficacy against HIV for a wide range of disinfectants and detergents, the evidence for some claims is equivocal.

Fresh aqueous solutions of sodium hypochlorite or troclosene sodium are recommended for general surface disinfection. If contaminated by blood, the concentration must be equivalent to 10 000 ppm of available chlorine. For non-corrosive disinfection of delicate items such as fibreoptic endoscopes, freshly activated alkaline glutaral 2% may be used following thorough washing (but see also Disinfection of Endoscopes, above). If a sterile body cavity will be entered the endoscope must be immersed for a minimum of 3 hours; otherwise a minimum of 30 minutes is sufficient, or 1 hour if the presence of *Mycobacterium tuberculosis* is suspected.

1. DoH. *UK Health Departments guidance for clinical health care workers: protection against infection with blood-borne viruses: recommendations of the expert advisory group on AIDS and the advisory group on hepatitis* (April 1998). Available at: http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4014474.pdf (accessed 27/08/08)

Disinfection of water

Travellers to regions of the world where water is not disinfected at source should be advised to boil or chemically sterilise water for drinking, cleaning teeth, and washing fruit and vegetables.[1] Chlorine and chlorine-releasing disinfectants including tosylchloramide sodium, halazone, sodium hypochlorite, and troclosene sodium are commonly used to sterilise **drinking water**. Iodine-releasing disinfectants such as tetraglycine hydroperiodide, or iodine itself may be useful for short-term or emergency disinfection of small volumes of water.[2] Organic material suspended in the water may reduce the available halogen concentration, and cloudy water should be filtered or allowed to settle and decanted before treatment. Emergency treatment of drinking water with lemon juice has been suggested during epidemics of waterborne gastro-enteritis.[3]

Chlorine and chlorine-releasing disinfectants are also used for recreational and therapeutic **bathing pools**, often with ozone.[4,5] Bromine-based disinfectants and ultraviolet radiation may also be used.

Legionnaires' disease (p. 188.2) is commonly transmitted via cooling water in **air conditioning** systems or **hot water** supplies. Hyperchlorination has been attempted to eradicate the organism from contaminated water sources but has been largely ineffective[6,7] and is no longer recommended. Other disadvantages of using chlorine-based systems at these temperatures and concentrations are corrosion of the plumbing system[7] and the production of potentially carcinogenic byproducts.[8] Effective disinfection can be achieved by raising and maintaining the water temperature above 50 degrees, ultraviolet light, and copper-silver ionisation.

Haemodialysis patients are exposed to large quantities of municipal drinking water as it is used for the production of **dialysis** fluids and may also be used for dialyser rinsing and reuse. Many of the chemical substances in the water, such as calcium, sodium, aluminium, chloramines, fluoride, copper, zinc, sulfates, and nitrates are potentially dangerous for dialysis patients, and can lead to acute or chronic poisoning. There is also a microbiological risk associated with the control of bacterial growth in the water treatment and distribution system. Contaminants are therefore removed by water purification systems. Water is pre-treated with activated carbon filters to remove chlorine and its derivatives and other suspended particles, and the hardness of the water is decreased with sodium exchange cationic resins, which remove calcium and magnesium. The final purification process then involves the removal of dissolved salts, bacteria, and endotoxins by reverse osmosis. Reverse osmosis membranes need to be regularly disinfected with chemical agents (such as hypochlorite and peracetic acid), heat, or ozone.[9]

1. Backer H. Water disinfections for international and wilderness travelers. *Clin Infect Dis* 2002; 34: 355–64.
2. WHO. Guidelines for drinking-water quality, third edition, incorporating first addendum: volume 1— recommendations. Geneva: WHO, 2006. Available at: http://www.who.int/water_sanitation_health/dwq/gdwq3/en/print.html (accessed 27/08/08)
3. D'Aquino M, Teves SA. Lemon juice as a natural biocide for disinfecting drinking water. *Bull Pan Am Health Organ* 1994; 28: 324–30.
4. Dadswell JV. Managing swimming, spa, and other pools to prevent infection. *Commun Dis Rep* 1996; 6 (review 2): R37–R40.
5. WHO. Guidelines for safe recreational water environments: volume 2—swimming pools and similar recreational environments. Geneva: WHO, 2006.
6. Kurtz JB, *et al.* Legionella pneumophila in cooling water systems: report of a survey of cooling towers in London and a pilot trial of selected biocides. *J Hyg (Camb)* 1982; 88: 369–81.
7. Helms CM, *et al.* Legionnaires' disease associated with a hospital water system: a five-year progress report on continuous hyperchlorination. *JAMA* 1988; 259: 2423–7.
8. Morris RD, *et al.* Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health* 1992; 82: 955–63.
9. Pontoriero G, *et al.* The quality of dialysis water. *Nephrol Dial Transplant* 2003;18 (suppl 7): vii21–vii5.

Hand hygiene

Hospital-acquired infections, including those due to multidrug-resistant pathogens, such as meticillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Staph. aureus*, and vancomycin-resistant enterococci, are a major problem in healthcare facilities.[1] Hand hygiene is one of the most important factors in preventing such infections, as it prevents transmission of pathogens by contact and the faecal-oral route. However, healthcare workers frequently do not wash their hands, and compliance rarely exceeds 40%.[2] A randomised study[3] to compare the efficacy of an alcohol-based solution for hand rubbing with hand washing with a medicated soap in reducing bacterial hand contamination during routine patient care found that the alcohol-based solution was significantly more effective (83% reduction versus 58%). The authors considered that the difference in efficacy might have been due to the duration of hand washing. Participants rubbed or washed their hands for about 30 seconds, but the recommended duration for hand washing is 30 seconds to 1 minute, a time that was adhered to in less than 35% of instances.

Some recommend[1,2] that alcohol-based hand rubs should replace hand washing as the standard for hand hygiene in all situations in which the hands are not visibly soiled. The basis for this is that hand rubbing requires less time, is microbiologically more effective, and is less irritating to skin than traditional hand washing with soap and water. Guidelines in the UK[4] and USA[5] do suggest alcohol as an alternative to soap and water in such situations but note that soap and water must be used if hands are visibly soiled. In addition, US guidelines advise[5] hand washing with a non-antimicrobial or antimicrobial soap and water when hands are contaminated with proteinaceous material, blood, or other body fluids and if exposure to *Bacillus anthracis* is suspected or proven. Alcohols, chlorhexidine, iodophores, and other antiseptic agents are not recommended for *B. anthracis* contamination as they have poor activity against the spores. Decontamination of the hands with an antiseptic hand rub or hand wash should occur before direct contact with patients, and before putting on sterile gloves when inserting catheters or other invasive devices that do not require a surgical procedure. Decontamination of the hands should also occur after contact with a patient's intact or non-intact skin, body fluids, mucous membranes, and wound dressings if hands are not visibly soiled. Hands should be decontaminated if moving from a contaminated body site to a clean body site during patient care, after contact with inanimate objects (including medical equipment) in the immediate vicinity of the patient, and after removing gloves. When performing surgical procedures hand hygiene with either an antimicrobial soap or an alcohol-based hand rub with persistent activity is recommended before putting on sterile gloves.

US guidelines[5] considers that the best antimicrobial efficacy can be achieved with alcohol (ethanol), isopropyl alcohol, and propyl alcohol, as their activity is broad and they are fast acting. Ethanol at high concentrations is the most effective treatment against non-enveloped viruses, whereas propyl alcohol seems to be more effective against the resident bacterial flora. Combinations of alcohols may have a synergistic effect. The antimicrobial efficacy of chlorhexidine (2 to 4%) and triclosan (1 to 2%) is both lower and slower. Bacterial resistance may occur, although the risk is higher for chlorhexidine than triclosan. Even if used with hand washing, they are still less effective than the alcohols. Plain soap and water has the lowest efficacy of all.

1. Tramuzz A, Widmer AF. Hand hygiene: a frequently missed lifesaving opportunity during patient care. *Mayo Clin Proc* 2004; 79: 109–16.
2. Widmer AF. Replace hand washing with use of a waterless alcohol hand rub? *Clin Infect Dis* 2000; 31: 136–43.
3. Girou E, *et al.* Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. *BMJ* 2002; 325: 362–6.
4. Cola JE, *et al.* Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect* 2006; 63 (suppl 1): S1–S44. Available at: http://www.his.org.uk/_db/_documents/MRSA_Guidelines_PDF.pdf (accessed 14/05/10)
5. CDC. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 2002; 51 (RR-16): 1–45. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf (accessed 15/03/06)

Injection site and catheter care

The need to disinfect the skin before injection is controversial.[1] Routine skin preparation of the injection site by swabbing with antiseptic has been reported to be both ineffective and unnecessary.[2,3] Central venous and arterial catheters, however, require the application of strict aseptic technique and injection site antisepsis to reduce the chance of infection.[4] Disinfection of catheter insertion sites with aqueous chlorhexidine 2% has been reported to be associated with fewer local and systemic infections than site preparation with either 10% povidone-iodine solution or 70% isopropyl alcohol,[5] although this has been challenged.[6] A subsequent study reported lower rates of catheter colonisation and catheter-related infection with an alcoholic solution of chlorhexidine 0.25% and benzalkonium chloride 0.025% than with povidone-iodine 10%.[7] In a study in preterm infants, technique had greater influence on bacterial counts at injection sites than the antiseptic used; chlorhexidine 0.5% in isopropyl alcohol and aqueous povidone-iodine 10% were equally effective, but cleansing with alcoholic chlorhexidine for 30 seconds or for two 10-second periods was more effective than cleansing for 5 or 10 seconds.[8]

The use of catheters impregnated with antiseptics or antibacterials has also been studied. Catheters impregnated with chlorhexidine and sulfadiazine silver on the external luminal surface, appear to be effective in reducing both catheter colonisation and related bloodstream infection in high-risk patients when used within 14 days.[9] Central venous catheters impregnated with minocycline and rifampicin have been reported to be associated with a lower infection rate than standard silicone catheters[10] and those impregnated with chlorhexidine and sulfadiazine silver.[11]

Guidelines have been produced for the prevention of infection associated with both peripheral intravascular and central venous catheterisation.[12-14]

1. Ayliffe GAJ, *et al. Chemical disinfection in hospitals.* 2nd ed. London: PHLS, 1993.
2. Dann TC. Routine skin preparation before injection: an unnecessary procedure. *Lancet* 1969; ii: 96–8.
3. Llauw J, Archer GJ. Swabaholics? *Lancet* 1995; 345: 1648.
4. Shepherd A, Williams N. Care of long-term central venous catheters. *Br J Hosp Med* 1994; 51: 598–602.
5. Maki DG, *et al.* Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet* 1991; 338: 339–43.
6. Segura M, Sitges-Serra A. Intravenous catheter sites and sepsis. *Lancet* 1991; 338: 1218.
7. Mimoz O, *et al.* Prospective, randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Crit Care Med* 1996; 24: 1818–23.
8. Malathi I, *et al.* Skin disinfection in preterm infants. *Arch Dis Child* 1993; 69: 312–16.
9. Veenstra DL, *et al.* Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA* 1999; 281: 261–7.
10. Hanna H, *et al.* Long-term silicone central venous catheters impregnated with minocycline and rifampin decrease rates of catheter-related bloodstream infection in cancer patients: a prospective randomized clinical trial. *J Clin Oncol* 2004; 22: 3163–71.
11. Darouiche RO, *et al.* A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 1999; 340: 1–8.
12. DoH. Guidelines for preventing infections associated with the insertion and maintenance of central venous catheters. *J Hosp Infect* 2001; 47 (suppl): S47–S67. Also available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005481?IdcService=GET_FILE&dID=140806&Rendition=Web (accessed 27/08/08)
13. O'Grady NP, *et al.* Guidelines for the prevention of intravascular catheter-related infections. *MMWR* 2002; 51 (RR-10): 1–29. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5110.pdf (accessed 15/03/06)
14. NICE. Infection control: prevention of healthcare-associated infections in primary and community care (June 2003). Section 5: central venous catheterisation. Available at: http://www.nice.org.uk/nicemedia/pdf/Infection_control_fullguideline.pdf (accessed 27/08/08)

Pre-operative skin disinfection

Skin preparation with antiseptics before surgery is generally carried out in an attempt to reduce the risks of surgical infection (see p. 209.1), but the evidence base for the practice is conflicting. The CDC recommends[1] pre-operative cleaning of skin at the incision site with either iodophores (e.g. povidone-iodine), alcohol-containing products, or chlorhexidine gluconate. While alcohol is considered to be the most effective and rapidly acting skin antiseptic, there are no appropriate studies to assess comparative efficacy. Furthermore, an analysis[2] of randomised studies comparing the use of pre-operative skin antiseptics with no antiseptics and studies comparing different skin antiseptics, found that there was insufficient evidence to conclude whether pre-operative skin antiseptics were effective in preventing postoperative surgical wound infection.

1. Mangram AJ, *et al.* CDC Hospital Infection Control Practices Advisory Committee. Guideline for prevention of surgical site infection, 1999. *Am J Infect Control* 1999; 27: 97–132. Also available at: http://www.cdc.gov/ncidod/dhqp/pdf/guidelines/SSI.pdf (accessed 15/03/06)
2. Edwards PS, *et al.* Preoperative skin antiseptics for preventing surgical wound infections after clean surgery. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2004 (accessed 06/04/10).

Wound disinfection

Antiseptic preparations are widely used to treat or prevent superficial infections and wounds, but their usefulness on broken skin and wounds has been questioned.[1] For further information on wound care, see p. 1690.1. Chlorine-releasing antiseptic solutions are generally regarded as irritant and although there is little direct evidence in patients there is concern that they may delay wound healing. Cetrimide,[2] tosylchloramide sodium,[3] hydrogen peroxide 3%,[4] iodophores,[4] and sodium hypochlorite solutions[2] are all reported to be cytotoxic *in vitro* or in *animal* models. Long-term or repeated use of these antiseptics for wound cleaning should probably be avoided. Chlorhexidine is relatively non-toxic.[2,3]

1. Brown CD, Zitelli JA. A review of topical agents for wounds and methods of wounding: guidelines for wound management. *J Dermatol Surg Oncol* 1993; 19: 732–7.
2. Thomas S, Hay NP. Wound cleansing. *Pharm J* 1985; 2: 206.
3. Brennan SS, *et al.* Antiseptic toxicity in wounds healing by secondary intention. *J Hosp Infect* 1986; 8: 263–7.
4. Lineweaver W, *et al.* Topical antimicrobial toxicity. *Arch Surg* 1985; 120: 267–70.

Acridine Derivatives

Acridina, derivados.

Description. Acridine derivatives are a group of quinoline antimicrobial dyes structurally related to acridine.

Acriflavinium Chloride *(rINN)*

Acriflavine; Acriflavine Hydrochloride; Acriflavinii Chloridum; Acriflavinii Dichloridum; Acriflavinio, cloruro de; Acriflavinium, Chlorure d'; Akriflavinium-chlorid; Cloruro de acriflavinio; Акрифлавиния Хлорид.

A mixture of 3,6-diamino-10-methylacridinium chloride hydrochloride and 3,6-diaminoacridine dihydrochloride.

CAS — 8063-24-9; 65589-70-0.
ATC — R02AA13.
ATC Vet — QG01AC90; QR02AA13.
UNII — 1S73VW819C.

NOTE. The nomenclature is confusing. Acriflavinium Chloride is *rINN* but was also the *BP* name for Acriflavinium Monochloride (see below).

Acriflavinium Monochloride

Acriflavinii Monochloridum; Acriflavinio, monocloruro de; Acriflavinium, monochlorure d'; Akriflavinio monochlorida; Akriflaviniummonoklorid; Akriflaviniummonokloridi; Euflavini; Euflavin; Euflavine; Euflavinum; Neutral Acriflavine; Neutroflavin.

A mixture of 3,6-diamino-10-methylacridinium chloride and 3,6-diaminoacridine monohydrochloride. The latter is usually present to the extent of between 30 and 40%.

CAS — 68518-47-8.
ATC — D08AA03.
ATC Vet — QD08AA03.

NOTE. The nomenclature is confusing. Although the *BP* name was Acriflavinium Chloride this is also *rINN* for a related compound (see above).

Aminoacridine Hydrochloride *(BANM, rINNM)*

Aminacrine Hydrochloride (USAN); Aminacrine Hydrochloride; Aminoacridina, hidrocloruro de; Aminoacridine. Chlorhydrate d'; Aminoacridini Hydrochloridum; Hidrocloruro de aminoacridina; NSC-7571; Аминоакридина Гидрохлорид.

9-Aminoacridine hydrochloride monohydrate.

$C_{13}H_{10}N_2.HCl.H_2O$=248.7

CAS — 90-45-9 (aminoacridine); 134-50-9 (anhydrous aminoacridine hydrochloride).
ATC — D08AA02.
ATC Vet — QD08AA02.
UNII — OR5RM3Q5QL.

Ethacridine Lactate *(BANM, rINNM)*

Acrinol; Aethacridinium Lacticum; Etacridina, lactato de; Etakridilnilaktaatti; Etakridinlaktat; Etakridin-laktát; Etakridino laktatas; Etakrydyny mleczan; Éthacridine, lactate d'; Ethacridini Lactas; Ethakridin-laktát; Lactato de etacridina; Lactoacridine; Этакридина Лактат.

6,9-Diamino-2-ethoxyacridine lactate.

$C_{15}H_{15}N_3O.C_3H_6O_3$=343.4

CAS — 442-16-0 (ethacridine); 1837-57-6 (ethacridine lactate); 6402-23-9 (ethacridine lactate monohydrate).
ATC — B05CA08; D08AA01.
ATC Vet — QB05CA08; QD08AA01.
UNII — V5IL571C1T.

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), and *Jpn* describe the monohydrate.

Ph. Eur. 8: (Ethacridine Lactate Monohydrate). A yellow crystalline powder. Sparingly soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 2% solution in water has a pH of 5.5 to 7.0. Protect from light.

Proflavine Hemisulfate

Hemisulfato de proflavina; Neutral Proflavine Sulphate; Proflavina, hemisulfato de; Proflavine, Hémisulfate de; Proflavine Hemisulphate (pINNM); Proflavine Hemisulphate; Proflavini Hemisulfas; Профлавина Гемисульфат.

3,6-Diaminoacridine sulphate dihydrate.

$(C_{13}H_{11}N_3)_2H_2SO_4.2H_2O$=552.6

CAS — 92-62-6 (proflavine).

UNII — 27V8M747VB (proflavine hemisulfate); 2961Y60ATP (proflavine sulfate).

Profile

The acridine derivatives are slow-acting antiseptics. They are bacteriostatic against many Gram-positive bacteria but less effective against Gram-negative bacteria. They are ineffective against spores. Their activity is increased in alkaline solutions and is not reduced by tissue fluids.

The acridine derivatives have been used for the treatment of infected wounds or burns and for skin disinfection, although they have been largely superseded by other antiseptics or suitable antibacterials. Prolonged treatment may delay healing. They have also been used for the local treatment of ear, oropharyngeal, and genito-urinary infections.

Aminoacridine is reported to be non-staining and is used as the hydrochloride as eye drops in the treatment and prophylaxis of superficial eye infections.

Ethacridine lactate is included in some preparations for the treatment of diarrhoea. It has also been given by extra-amniotic injection for the termination of pregnancy (p. 2131.3) but other methods are usually preferred.

Other acridine derivatives covered elsewhere in *Martindale* include mepacrine (p. 935.2), which is used in the treatment of giardiasis, and pyronaridine (p. 664.3), which is used to treat malaria. Amsacrine (p. 741.3) is a 9-anilinoacridine drug that is used in the treatment of adult leukaemias. Other acridine derivatives have also been investigated as anticancer drugs because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes.

Hypersensitivity to acridine derivatives has been reported.

References.
1. Wainwright M. Acridine—a neglected antibacterial chromophore. *J Antimicrob Chemother.* 2001; 47: 1–13.
2. Denny WA. Acridine derivatives as chemotherapeutic agents. *Curr Med Chem* 2002; 9: 1655–65.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Aminopt†; ***China***: Bi Fen (彼芬); ***Ger.***: Metifex; Neochinosol; Rivanol; ***India***: Abrocin; Abortil; Emcredil†; Vecredil; ***Pol.***: Rivanol; Rivanolum; Rivel; Rywanol†; ***Turk.***: Rivanol.

Multi-ingredient Preparations. ***Arg.***: Carnot Topico; Nene Dent; Otocuril; ***Austral.***: Medijel; ***Austria***: Dermowund†; ***Braz.***: Acridin; Cystex; ***Chile***: Molca; ***Fr.***: Chromargon; Pyorex; ***Ger.***: Tannacomp; ***Hong Kong***: Medijel; ***Hung.***: Glycosept; ***India***: Emscab†; ***Irl.***: Aidex†; Medijel; ***Israel***: Medijel†; ***Malaysia***: Burnol Plus; Medijel; ***NZ***: Medijel; ***Pol.***: Septalan†; ***S.Afr.***: Achromide; Daromide†; Vagarsol; ***Singapore***: Burnol Plus; Medijel; ***Spain***: Antigrietun; Hepro; ***Switz.***: Haemolan†; Tyrothricin†; ***Thai.***: Burnol Plus; Flavinol; ***Turk.***: Derivit; Dervanol; ***UK***: Iglu; Medijel; ***USA***: Alasulf; Deltavac; DIT1-2.

Pharmacopoeial Preparations

BPC 1973: Proflavine Cream.

Alcohol ⊗

Aethanolum; Alcohol etílico; Alcool; Alkol; Etanol; Etanol (96%); Etanol bezwodny; Etanoli; Etanolis; Ethanol; Ethanolum; Ethyl Alcohol; Этанол; Алкоголь.

C_2H_5OH=46.07

CAS — 64-17-5.

ATC — D08AX08; V03AB16; V03AZ01.

ATC Vet — QD08AX08; QV03AB16; QV03AZ01.

UNII — 3K9958V90M.

Street names. The following terms have been used as 'street names' (see p. vii) or slang names for various forms of alcohol:

Booze; Drinks; Grog; Juice; Jungle juice; Liq; Liquor; Lunch head; Moonshine; Piss; Sauce; Schwillins.

Pharmacopoeias. Various strengths are included in *Br., Chin., Eur.* (see p. vii), *Int., Jpn, US,* and *Viet.* Also in *USNF.*

In *Martindale* the term alcohol is used for alcohol 95 or 96% v/v.

Ph. Eur. 8: (Ethanol, Anhydrous; Ethanolum Anhydricum; Ethanol BP 2014). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH at 20 degrees. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78 degrees. Miscible with water and with dichloromethane. Protect from light.

The BP 2014 gives Absolute Alcohol and Dehydrated Alcohol as approved synonyms.

Ph. Eur. 8: (Ethanol (96 per cent)). It contains not less than 95.1% v/v or 92.6% w/w and not more than 96.9% v/v or 95.2% w/w of C_2H_5OH at 20 degrees, and water. A colourless, clear, volatile, flammable, hygroscopic liquid; it burns with a blue, smokeless flame. B.p. about 78 degrees. Miscible with water and with dichloromethane. Protect from light.

The BP 2014 gives Alcohol (96 per cent) as an approved synonym.

BP 2014: (Dilute Ethanols). The monograph describes several dilute alcohols containing between 20 and 90% v/v of C_2H_5OH, and one of these, ethanol (90%), is also known as rectified spirit.

USP 36: (Alcohol). It contains not less than 92.3% w/w or 94.9% w/v and not more than 93.8% w/w or 96.0% w/v of C_2H_5OH at 15.56 degrees. A clear, colourless, mobile, volatile liquid with a characteristic odour and burning taste; it is flammable. B.p. about 78 degrees. Miscible with water and with almost all other organic solvents. Store in airtight containers. Protect from light.

USP 36: (Dehydrated Alcohol). It contains not less than 99.5% v/v or 99.2% w/w of C_2H_5OH (sp. gr. not more than 0.7962 at 15.56 degrees). Store in airtight containers. Protect from light.

USNF 31: (Diluted Alcohol). It contains 48.4 to 49.5% v/v or 41 to 42% w/w of C_2H_5OH. Store away from fire in airtight containers.

Alcoholic strength. This is expressed as a percentage by volume of alcohol. It was previously often expressed in terms of *proof spirit*. Proof spirit contained about 57.1% v/v or 49.2% w/w of C_2H_5OH, and was defined as 'that which at the temperature of 51 degreesF weighs exactly twelve-thirteenths of an equal measure of distilled water'. Spirit of such a strength that 100 volumes contained as much ethyl alcohol as 160 volumes of proof spirit was described as '60 OP' (over proof). Spirit of which 100 volumes contained as much alcohol as 40 volumes of proof spirit was described as '60 UP' (under proof).

An alternative method of indicating spirit strength was used on the labels of alcoholic beverages in the UK when the strength was given as a number of degrees, proof spirit being taken as 100 degrees. In the USA alcoholic strength is expressed in degrees, the value of which is equal to twice the percentage by volume. Thus 70 degrees proof (old UK system) is equivalent to 40% v/v, and therefore to 80 degrees proof (USA system).

Uses and Administration

Alcohol has been used and abused for many thousands of years, in the form of alcoholic beverages, for its effects on the CNS. However, it also has pharmaceutical applications.

Alcohol is bacteriostatic at low concentrations but has bactericidal activity at higher concentrations; it does not, however, destroy bacterial spores. The mechanism of action appears to be denaturation of proteins. In the total absence of water, proteins are not denatured as rapidly as when water is present. Its bactericidal activity drops sharply when diluted below a 50% concentration and the optimal bactericidal concentration is 60 to 90% by volume. Alcohol also has some fungicidal and virucidal activity. It is used to disinfect skin before injection, venepuncture, or surgical procedures. It is also used to disinfect hands and clean surfaces. A concentration of 70%, often as methylated spirits (p. 1760.3), is commonly used for disinfection. Alcohol should not be used for disinfection of surgical or dental instruments because of its low efficacy against bacterial spores and inability to penetrate protein-rich materials.

Alcohol also has anhidrotic, rubefacient, and astringent and haemostatic properties. It is sometimes used for its skin-cooling properties and to harden the skin. It is an ingredient of several topical preparations used for skin disorders.

Alcohol is widely used as a solvent and preservative in pharmaceutical preparations.

Alcohol may be used as a neurolytic in the management of severe and chronic pain.

Alcohol is given intravenously in the treatment of acute poisoning from ethylene glycol (p. 2500.3) and methyl alcohol (p. 2196.3).

Alcohol is also used in sclerotherapy.

Pain. The use of alcohol as a neurolytic to produce destructive nerve block (see under Pain, p. 1977.1) has produced variable results, and some consider the risk of complications outweighs the benefits. However, alcohol has been injected into the pituitary gland for relief of severe pain of the head and neck;[1,2] doses of 1 mL of absolute alcohol have been used.[1] It may be useful in coeliac plexus block, and has been injected into the muscle sheath to relieve painful muscle spasms in patients with multiple sclerosis.[1] Alcohol 50 to 100% may be used for peripheral or central nerve block in terminally ill patients with pain that does not respond to drug therapy;[3,4] the block produced by alcohol may occasionally last up to 2 years, even longer than that produced by phenol. However, larger volumes of alcohol than phenol are required, which means that blockade may be less precise due to leakage to proximal sites;[4] in addition, alcohol may exacerbate local pain on injection, because of its irritant effect on the tissues, and injection of a local anaesthetic beforehand, or giving the alcohol combined with a local anaesthetic, may be necessary.[4,5]

Intrathecal injection of alcohol has also been used for the intractable pain of spasticity (p. 2014.2); early use, as soon as spasticity becomes painful and disabling, has been advocated.[6]

1. Lloyd JW. Use of anaesthesia: the anaesthetist and the pain clinic. *BMJ* 1980; 281: 432–4.
2. Lipton S. Pain relief in active patients with cancer: the early use of nerve blocks improves the quality of life. *BMJ* 1989; 298: 37–8.
3. Hardy, PAJ. The role of the pain clinic in the management of the terminally ill. *Br J Hosp Med* 1990; 43: 142–6.
4. Gordin V, *et al.* Acute and chronic pain management in palliative care. *Best Pract Res Clin Obstet Gynaecol* 2001; 15: 203–34.
5. Kongsgaard UE, *et al.* Nevrolytisk blokade hos kreftpasienter–fortsatt en nyttig behandling. *Tidsskr Nor Laegeforen* 2004; 124: 481–3.
6. Viel E, *et al.* Spasticité: intérêt du testing par anesthésie locorégionale et blocs thérapeutiques. *Ann Fr Anesth Reanim* 2005; 24: 667–72.

Sclerotherapy. Alcohol has been used successfully as a sclerosant in a variety of conditions including aldosterone-producing adenoma,[1] parathyroid adenomas,[2] thyroid nodules,[3,4] advanced rectal cancer,[5] hepatocellular carcinoma,[6,7] dysphagia associated with oesophogastric cancer,[8,9] hepatic[10] or renal[11] cysts, and gallbladder obstruction.[12] It has also been used in the sclerotherapy of oesophageal varices,[13,14] although the safety of this procedure has been questioned after a report of complications developing in 13 of 17 patients, 2 of whom died.[15] Other conditions in which alcohol has been used as a sclerosant include bleeding from ruptured hepatomas[16] and in peptic ulcer disease,[17] vascular malformations,[18] and obstructive cardiomyopathies[19] resistant to usual treatment.

Other sclerosants used in oesophageal varices are discussed on p. 2563.1.

1. Hokotate H, *et al.* Aldosteronomas: experience with superselective adrenal arterial embolization in 33 cases. *Radiology* 2003; 227: 401–6.
2. Vergès B, *et al.* Traitement des adénomes parathyroïdiens par alcoolisation sous contrôle échographique. *Ann Chir* 2000; 125: 457–60.
3. Monzani F, *et al.* Autonomous thyroid nodule and percutaneous ethanol injection. *Lancet* 1991; 337: 743.
4. Bennedbaek FN, Hegedüs L. Alcohol sclerotherapy for benign solitary solid cold thyroid nodules. *Lancet* 1995; 346: 1227.
5. Payne-James J, *et al.* Advanced rectal cancer. *BMJ* 1990; 300: 746.
6. Lencioni R, *et al.* Alcoolizzazione percutanea dell'epatocarcinoma: risultati a lungo termine. *Radiol Med (Torino)* 1997; 94: 8–13.
7. Ebara M, *et al.* Percutaneous ethanol injection for small hepatocellular carcinoma: therapeutic efficacy based on 20-year observation. *J Hepatol* 2005; 43: 458–64.
8. Payne-James JJ, *et al.* Use of ethanol-induced tumor necrosis to palliate dysphagia in patients with esophagogastric cancer. *Gastrointest Endosc* 1990; 36: 43–6.
9. Stanners AJ, *et al.* Alcohol injection for palliation of malignant oesophageal disease. *Lancet* 1993; 341: 767.
10. Larsen TB, *et al.* Single-session alcohol sclerotherapy in symptomatic benign hepatic cysts: long-term results. *Acta Radiol* 1999; 40: 636–8.
11. Mohsen T, Gomha MA. Treatment of symptomatic simple renal cysts by percutaneous aspiration and ethanol sclerotherapy. *BJU Int* 2005; 96: 1369–72.
12. Asfar S, *et al.* Percutaneous sclerosis of gallbladder. *Lancet* 1989; ii: 387.
13. Meirelles-Santos JO, *et al.* Absolute ethanol and 5% ethanolamine oleate are comparable for sclerotherapy of esophageal varices. *Gastrointest Endosc* 2000; 51: 573 6.
14. Ferrari AP, *et al.* Efficacy of absolute alcohol injection compared with band ligation in the eradication of esophageal varices. *Arq Gastroenterol* 2005; 42: 72–6.
15. Bhargava DK, *et al.* Endoscopic sclerotherapy using absolute alcohol. *Gut* 1986; 27: 1518.
16. Chung SCS, *et al.* Injection of alcohol to control bleeding from ruptured hepatomas. *BMJ* 1990; 301: 421.
17. Lin HJ, *et al.* Heat probe thermocoagulation and pure alcohol injection in massive peptic ulcer haemorrhage: a prospective, randomised controlled trial. *Gut* 1990; 31: 753–7.
18. Deveikis JP. Percutaneous ethanol sclerotherapy for vascular malformations in the head and neck. *Arch Facial Plast Surg* 2005; 7: 322–5.
19. Knight CJ. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy. *Heart* 2006; 92: 1339–44.

Adverse Effects

Adverse effects of alcohol arise chiefly from the intake of alcoholic beverages. The concentration of alcohol in the blood producing a state of intoxication varies between individuals.

- Low concentrations (up to 180 mg per 100 mL) of alcohol may result in impaired vision, reaction time, and coordination and emotional lability.
- At low to moderate concentrations (180 to 350 mg per 100 mL), alcohol acts as an apparent stimulant; depression of cortical function causes loss of judgement, slurred speech, diplopia, blurred vision, ataxia, lack of

coordination, blackouts, sweating, tachycardia, nausea, vomiting, and incontinence. Alcohol inhibits the release of antidiuretic hormone resulting in enhanced diuresis. Acidosis (especially in children), hypoglycaemia, and hypokalaemia may occur.

- High concentrations (350 to 450 mg per 100 mL) of alcohol result in cold clammy skin, hypothermia, hypotension, stupor, coma, dilated pupils, and depressed or absent tendon reflexes. Severe hypoglycaemia, convulsions, respiratory depression, and metabolic acidosis may occur. Cardiac arrhythmias such as atrial fibrillation and AV block have been recorded.

The median lethal blood-alcohol concentration is generally estimated to be about 400 to 500 mg per 100 mL. Death may occur at lower blood-alcohol concentrations due to inhalation of vomit during unconsciousness.

Chronic excessive consumption of alcohol may cause damage to many organs, particularly the brain and the liver. Possible direct toxic effects of alcohol on the brain, as well as thiamine deficiency, may lead to Wernicke-Korsakoff syndrome. Fat deposits may occur in the liver and there may be a reduction in various blood cell counts. Nutritional diseases may occur due to inadequate diet. High alcohol consumption has been associated with pancreatitis, and an increased risk of cardiovascular disease, although some consider that moderate consumption might have a protective effect against ischaemic heart disease.

Alcohol consumption has also been associated with an increased risk of some types of cancer.

The term '**alcoholism**' may be used to denote dependence on alcohol, which is of the barbiturate-alcohol type (see Amobarbital, p. 1038.1) and usually involves tolerance to other sedatives and anaesthetics. After prolonged periods of excessive alcohol consumption, a drop in blood-alcohol concentration may precipitate a withdrawal syndrome characterised by tremor, agitation, feelings of dread, nausea, vomiting, and sweating; hallucinations, seizures, and delirium tremens may also develop.

A **fetal alcohol syndrome** may be noted in infants born to alcoholic mothers; such infants have a distinctive set of facial anomalies, growth retardation, and significant learning and/or behavioural problems. There have been some reports of the syndrome and other adverse effects on the fetus being associated with moderate alcohol intake in pregnancy. It is therefore generally suggested that alcohol is avoided, or at least intake limited, during pregnancy (see Pregnancy, p. 1735.1).

Frequent application of alcohol to the skin produces irritation and dry skin.

Effects on the skin. A 70% solution of alcohol, containing povidone-iodine, caused partial thickness chemical burns beneath tourniquets in 3 young children.[1] Other adverse effects on the skin reported with the topical application of alcohols have included necrosis after skin cleansing of preterm neonates with methylated spirits[2,3] and haemorrhagic skin necrosis due to the alcohol content of chlorhexidine in spirit used as a disinfectant in umbilical artery catheterisation in preterm infants.[4]

See also Children, under Adverse Effects of Isopropyl Alcohol, p. 1759.1.

1. Dickinson JC, Bailey BN. Chemical burns beneath tourniquets. *BMJ* 1988; **297**: 1513.
2. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; **57**: 477–9.
3. Murch S, Costelloe K. Hyperosmolality related to propylene glycol in an infant. *BMJ* 1990; **301**: 389.
4. Al-Jawad ST. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1983; **58**: 395–6.

Treatment of Adverse Effects

Treatment of acute poisoning with alcohol should include hydration with intravenous fluids, control of nausea and vomiting, and correction of electrolyte imbalances, such as hypomagnesaemia. Protection of the airway is crucial and ventilation may be required in cases of respiratory depression. Glucose is indicated for patients with hypoglycaemia, while thiamine supplementation should be considered for chronic alcoholics. Hypothermia and hypotension should be corrected. Convulsions may be controlled with intravenous benzodiazepines or phenytoin. Haemodialysis is of value in severe alcohol poisoning. Gut decontamination and activated charcoal are unlikely to be of benefit due to the rapid absorption of alcohol through intestinal mucosa. The use of intravenous infusions of fructose to treat severe alcohol poisoning is not recommended.

The management of the alcohol withdrawal syndrome and long-term abstinence following withdrawal are discussed below.

Alcohol withdrawal and abstinence. The alcohol withdrawal syndrome presents in the early stages as a classical hyperadrenergic state with tremor, tachycardia, sweating, and hypertension. Sometimes this is accompanied by mild disorientation, anxiety, impaired concentration, depression, agitation, and gastrointestinal symptoms. Insomnia, nightmares, and transient hallucinations can also be present. The condition may be self-limiting without the need for therapeutic intervention or it may progress to the severe and potentially fatal condition of delirium tremens (DTs), often characterised by delirium, disorientation, and hallucinations. In some cases generalised tonic-clonic seizures occur within 24 hours of alcohol withdrawal and are followed by delirium tremens.

The general management of the alcohol **withdrawal** syndrome and maintenance of abstinence have been the subject of many reviews and discussions.[1-17] In most cases symptoms do not require treatment and disappear within a few days, but more severe cases may require managed withdrawal from alcohol to avoid complications.

Benzodiazepines are usually the drugs of first choice because of their sedative, anxiolytic and anticonvulsant properties. If given promptly, benzodiazepines can prevent progression to seizures and delirium tremens. Longer-acting drugs such as chlordiazepoxide or diazepam may be more effective against withdrawal seizures and provide smoother withdrawal, while shorter-acting ones such as lorazepam or oxazepam have a smaller risk of producing oversedation and may be more suitable for use in the elderly and, since they do not rely on hepatic enzymes for their metabolism, for patients with liver disease. Because of the risk of dependence benzodiazepines should only be given in short courses. Some advocate that benzodiazepine dosage should be adjusted according to the severity of symptoms with special care being paid to patients with a history of withdrawal seizures, comorbid conditions, or those using sedative or hypnotic medication. This reduces the amount of drug required and the duration of treatment but entails regular monitoring by trained nursing staff. For mild to moderate symptoms, standard anxiolytic or muscle-relaxing oral doses of benzodiazepines may be sufficient. For severe symptoms, or for the treatment of delirium tremens, higher doses and use of the intravenous route may be required. *Clomethiazole* appears to be an effective alternative to the benzodiazepines (but see under Interactions of Clomethiazole, p. 1055.1); although widely used in Europe, it is not available in the USA. Some centres use phenobarbital but *barbiturates* are generally not recommended for the treatment of alcohol withdrawal syndrome.

Antipsychotics are not usually recommended for use in the control of symptoms of alcohol withdrawal since they do not reduce delirium tremens and some may reduce the seizure threshold. However, they might be considered for use as adjuncts in patients requiring treatment of marked agitation or hallucinations.

The generalised tonic-clonic seizures associated with alcohol withdrawal are usually self-limiting and patients who have only one or two seizures do not usually require any specific treatment beyond continuing therapy with benzodiazepines or clomethiazole. For recurrent seizures or status epilepticus (p. 510.2) a benzodiazepine may be given intravenously. Other types of seizure may be associated with head trauma or pre-existing seizure disorders (p. 506.1) and should be treated accordingly. Other *antiepileptics* such as carbamazepine have been tried in the treatment of alcohol withdrawal seizures and may be of use as adjuncts in controlling other symptoms of alcohol withdrawal syndrome. As benzodiazepines are effective in preventing withdrawal seizures, other prophylactic drugs are not usually indicated.

Beta blockers can reduce symptoms of autonomic overactivity such as tachycardia, hypertension, tremor, and agitation but because they can mask these symptoms of withdrawal and do not prevent the development of more serious complications they should not be used alone. Some beta blockers such as propranolol that penetrate the CNS may produce CNS effects that complicate therapy. The alpha$_2$-adrenoceptor agonist *clonidine* may be of similar benefit as an adjunct.

Other drugs that have been reported to be of benefit in alcohol withdrawal syndrome include baclofen, nitrous oxide, and gamma-hydroxybutyrate.

It is essential that in all cases of alcohol withdrawal syndrome hypoglycaemia, dehydration, electrolyte disturbances (in particular magnesium), and vitamin deficiencies be corrected. However, hydration should be undertaken with care as alcoholics may be more prone to develop cerebral oedema, the management of which is discussed under Raised Intracranial Pressure on p. 1271.3. It is usually recommended that all patients should be given thiamine because of their increased risk of developing Wernicke-Korsakoff syndrome (p. 2103.3). It should be noted that giving intravenous glucose before thiamine may precipitate Wernicke's encephalopathy in thiamine-deficient patients.

Abstinence. Once the initial acute withdrawal of alcohol is achieved treatment may be required to maintain long-term abstinence. Pharmacotherapy should only be used as an adjunct to psychotherapy and supportive care. Drugs used to modify alcohol seeking behaviour either sensitise the patient to alcohol (aversive drugs) or reduce or alleviate the craving for alcohol. The main ones used for aversive therapy have historically been *disulfiram* and *calcium carbimide*. A patient who ingests alcohol after taking an adequate dose of one of these drugs will have a severe and unpleasant reaction (see Adverse Effects of Disulfiram, p. 2496.1). However, the deterrent value of aversive drugs, and their potential toxicity, has long been a matter of debate. Such treatment is likely to be of little use unless it is undertaken with the willing cooperation of the patient and is used with psychotherapy, and even then there is no evidence that it has any effect on the long-term course of alcoholism.

Of those drugs that have been reported to reduce alcohol craving *acamprosate* and *naltrexone* have been the most promising as adjuncts for management of alcohol dependence and have been shown to improve abstinence and reduce relapse rates. Whether benefit is maintained long-term after treatment is stopped is unclear. *Nalmefene* is also used to help reduce the level of alcohol consumption in patients who have a high drinking risk. *Other drugs* tried with varying benefit include aripiprazole, tiapride, baclofen, gamma-hydroxybutyrate, bromocriptine, and topiramate. Experimental evidence suggests that serotonin plays a role in the impulsivity and craving and is partly responsible for alcohol dependence. However, studies with SSRIs in alcohol dependence have been disappointing and it would appear that the benefit is in treating underlying depression rather than influencing drinking behaviour. Similar results have been noted with other drugs acting at serotonin receptors such as buspirone, ritanserin, and nefazodone. However, studies with ondansetron have shown some efficacy on drinking frequency and intake.

1. Mayo-Smith MF. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. Pharmacological management of alcohol withdrawal: a meta-analysis and evidence-based practice guideline. *JAMA* 1997; **278**: 144–51.
2. O'Connor PG, Schottenfeld RS. Patients with alcohol problems. *N Engl J Med* 1998; **338**: 592–602.
3. Tinsley JA, *et al.* Developments in the treatment of alcoholism. *Mayo Clin Proc* 1998; **73**: 857–63.
4. Schaffer A, Naraiyo CA. Recommended drug treatment strategies for the alcoholic patient. *Drugs* 1998; **56**: 571–85.
5. Naik PC, Brownell LW. Treatment of psychiatric aspects of alcohol misuse. *Hosp Med* 1999; **60**: 173–7.
6. Garbutt JC, *et al.* Pharmacological treatment of alcohol dependence: a review of the evidence. *JAMA* 1999; **281**: 1318–25.
7. Swift RM. Drug therapy for alcohol dependence. *N Engl J Med* 1999; **340**: 1482–90.
8. Kraemer KL, *et al.* Managing alcohol withdrawal in the elderly. *Drugs Aging* 1999; **14**: 409–25.
9. Myrick H, *et al.* New developments in the pharmacotherapy of alcohol dependence. *Am J Addict* 2001; **10** (suppl): 3–15.
10. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. *N Engl J Med* 2003; **348**: 1786–95.
11. Mayo-Smith MF, *et al.* Management of alcohol withdrawal delirium: an evidence-based practice guideline. *Arch Intern Med* 2004; **164**: 1405–12.
12. Mann K. Pharmacotherapy of alcohol dependence: a review of the clinical data. *CNS Drugs* 2004; **18**: 485–504.
13. Kenna GA, *et al.* Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 1. *Am J Health-Syst Pharm* 2004; **61**: 2272–9.
14. Kenna GA, *et al.* Pharmacotherapy, pharmacogenomics, and the future of alcohol dependence treatment, part 2. *Am J Health-Syst Pharm* 2004; **61**: 2380–8.
15. Kiefer F, Mann K. New achievements and pharmacotherapeutic approaches in the treatment of alcohol dependence. *Eur J Pharmacol* 2005; **526**: 163–71.
16. Ait-Daoud N, *et al.* An overview of medications for the treatment of alcohol withdrawal and alcohol dependence with an emphasis on the use of older and newer anticonvulsants. *Addict Behav* 2006; **31**: 1628–49.
17. Leggio L, *et al.* New developments for the pharmacological treatment of alcohol withdrawal syndrome: a focus on non-benzodiazepine GABAergic medications. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; **32**: 1106–17.

Precautions

Excessive alcohol intake should be avoided. In the UK, the DoH advises that men should not drink more than 3 to 4 units of alcohol daily, and women not more than 2 to 3 units of alcohol daily, regardless of whether one drinks every day, once or twice a week, or occasionally. A unit of alcohol is defined as 10 mL of pure alcohol. A normal measure of spirits in a public house contains about 1 unit of alcohol. A pint of ordinary strength lager or cider, a pint of bitter, or 175 mL glass of wine contain about 2 units of alcohol, while a pint of strong lager contains about 3 units of alcohol. Women and the elderly may be more susceptible to the adverse effects of alcohol ingestion.

Alcohol may aggravate peptic ulcer disease or hepatic impairment and impair control of diabetes mellitus or epilepsy. Ingestion of alcohol during pregnancy or breast feeding is not advisable. In chronic alcoholics there may be tolerance to the effects of other CNS depressants including general anaesthetics.

All processes requiring judgement and coordination are affected by alcohol and these include the driving of any form of transport and the operating of machinery. It is an offence in many countries for motorists to drive when the blood-alcohol concentration is above a stated value while in some countries any detectable concentration is an offence.

The alcohol concentration in urine and expired air can be used to estimate the blood-alcohol concentration.

It should be remembered that alcohol may be present in pharmaceutical preparations such as elixirs and mouthwashes, and that children may be particularly susceptible to its hypoglycaemic effects.

Breast feeding. The American Academy of Pediatrics[1] states that, although usually compatible with breast feeding, ingestion of large amounts of alcohol by a breast-feeding mother may cause drowsiness, diaphoresis, deep sleep, weakness, decrease in linear growth, and abnormal weight gain in the infant; maternal ingestion of 1 g/kg or more daily decreases the milk ejection reflex.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Driving. In addition to the legal maximum blood-alcohol concentration permitted for motorists, in the UK there are restrictions on holding a driving licence for those who persistently misuse alcohol, have alcohol dependency, have had an alcohol-related seizure, or have an alcohol-related disorder.[1]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued November 2013). Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/258991/aagv1.pdf (accessed 20/11/13)

Porphyria. Alcohol has been associated with acute attacks of porphyria and alcohol consumption should be avoided in porphyric patients.

Reviews.
1. Doss MO. *et al.* Alcohol and porphyrin metabolism. *Alcohol Alcohol* 2000; 35: 109–25.

Pregnancy. Alcohol crosses the placenta and is both teratogenic and fetotoxic in humans.[1,2] Binge drinking or excessive alcohol intake is associated with low birthweight, behavioural and intellectual difficulties later in life, and fetal alcohol syndrome (see Adverse Effects, p. 1733.3). Alcohol consumption is also associated with an increased risk of miscarriage.[1] It is therefore generally agreed that pregnant women should avoid or limit their intake of alcohol although guidance from professional bodies has been slightly inconsistent.[3] In the UK, guidance from NICE[2] and the Royal College of Obstetricians and Gynaecologists[1] state that while the safest approach is to avoid any alcohol intake during pregnancy particularly the first trimester, there is no evidence of harm from infrequent or low levels of alcohol intake (no more than one or two units once or twice a week). However, in the USA, the Surgeon General's Office[4] and the American Academy of Pediatrics[5] advise women who are pregnant or women who are planning a pregnancy to avoid alcohol use completely.

1. Royal College of Obstetricians and Gynaecologists. RCOG Statement no. 5: alcohol consumption and the outcomes of pregnancy (issued March 2006). Available at: http://www.rcog.org.uk/files/rcog-corp/uploaded-files/RCOGStatement5AlcoholPregnancy2006.pdf (accessed 19/09/06)
2. National Collaborating Centre for Women's and Children's Health/NICE. Antenatal care: routine care for the healthy pregnant woman (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG62FullGuidelineCorrectedJune2008July2009.pdf (accessed 19/03/10)
3. O'Leary CM, *et al.* A review of policies on alcohol use during pregnancy in Australia and other English-speaking countries. 2006. *Med J Aust* 2007; 186: 466–71.
4. United States Department of Health and Human Services. News release: U.S. Surgeon General releases advisory on alcohol use in pregnancy (issued 21st February 2005). Available at: http://surgeongeneral.gov/pressreleases/sg02222005.html (accessed 19/09/06)
5. American Academy of Pediatrics: Committee on Substance Abuse and Committee on Children With Disabilities. Fetal alcohol syndrome and alcohol-related neurodevelopmental disorders. *Pediatrics* 2000; 106: 358–61. Also available at: http://www.pediatrics.org/cgi/content/full/106/2/358 (accessed 19/09/06)

Interactions

Reports of interactions between alcohol and other drugs are not consistent, possibly because acute alcohol intake may inhibit drug metabolism while chronic alcohol intake can enhance the induction of drug-metabolising enzymes in the liver.

Alcohol can enhance the acute effects of CNS depressants, such as hypnotics, antihistamines, opioid analgesics, antiepileptics, antidepressants, antipsychotics, and sedatives. In addition 'dose dumping', rapid and potentially fatal release of high doses from modified-release formulations, has occurred when some opioid preparations were taken with alcohol.

Unpleasant reactions, similar to those occurring with disulfiram (p. 2496.1), may occur when alcohol is taken with chlorpropamide, griseofulvin, mepacrine, metronidazole and other nitroimidazoles, the nitrofuran derivatives furazolidone and nifuratel, procarbazine, or some cephalosporins. Alcoholic beverages containing tyramine may cause reactions when taken by patients receiving MAOIs.

Alcohol can cause hypoglycaemic reactions in patients receiving sulfonylurea antidiabetics or insulin, and orthostatic hypotension in patients taking drugs with a vasodilator action. It may enhance the hypotensive effects of antihypertensives and has also increased the sedative effect of indoramin. Alcohol may increase gastric bleeding caused by analgesics and can have a variable effect on oral anticoagulants. It may decrease the antidiuretic effect of vasopressin.

Reviews.
1. McInnes GT. Interactions that matter: alcohol. *Prescribers' J* 1985; 25: 87–90.
2. Lieber CS. Interaction of alcohol with other drugs and nutrients: implications for the therapy of alcoholic liver disease. *Drugs* 1990; 40 (suppl 3): 23–44.
3. Fraser AG. Pharmacokinetic interactions between alcohol and other drugs. *Clin Pharmacokinet* 1997; 33: 79–90.
4. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health* 1999; 23: 40–54.

Cycloserine. Increased blood-alcohol concentrations have been reported in patients receiving cycloserine.[1]

1. Glass P, *et al.* Beobachtungen und untersuchungen über die gemeinsame wirkung von alkohol und D-cycloserin. *Arzneimittelforschung* 1965; 15: 684–8.

Fomepizole. For the interaction between alcohol and fomepizole, see Interactions under Fomepizole, p. 1553.2.

H_2-antagonists. The existence of an interaction between H_2-antagonists and alcohol is controversial and has not been established. While some studies suggest that *cimetidine*[1-3] and *nizatidine*[3] can increase peak blood-alcohol concentrations the effects of *ranitidine*[2,4] have been variable; *famotidine* appears to have no significant effect.[2] Later studies report that any interaction between H_2-antagonists and alcohol is minor and unlikely to be of clinical importance.[5-8]

1. Caballeria J, *et al.* Effects of cimetidine on gastric alcohol dehydrogenase activity and blood ethanol levels. *Gastroenterology* 1989; 96: 388–92.
2. DiPadova C, *et al.* Effects of ranitidine on blood alcohol levels after ethanol ingestion: comparison with other H_2-receptor antagonists. *JAMA* 1992; 267: 83–6.
3. Holt S, *et al.* Evidence for an interaction between alcohol and certain H_2 receptor antagonists. *Gut* 1991; 32: A1220.
4. Toon S, *et al.* Lack of effect of high dose ranitidine on the post-prandial pharmacokinetics of alcohol. *Gut* 1992; 33 (suppl): S10.
5. Raufman J-P, *et al.* Histamine-2 receptor antagonists do not alter serum ethanol levels in fed, nonalcoholic men. *Ann Intern Med* 1993; 118: 488–94.
6. Levitt MD. Do histamine-2 receptor antagonists influence the metabolism of ethanol? *Ann Intern Med* 1993; 118: 564–5.
7. Kleine M-W, Eril D. Comparative trial in volunteers to investigate possible ethanol-ranitidine interaction. *Ann Pharmacother* 1993; 27: 841–5.
8. Gugler R. H_2-antagonists and alcohol: do they interact? *Drug Safety* 1994; 10: 271–80.

Paracetamol. The effects of paracetamol poisoning may be exacerbated by chronic alcohol consumption (see p. 116.2).

Verapamil. When verapamil has been taken with alcohol there has been a reported increase in peak blood-alcohol concentrations of about 17%.[1] Such an interaction may extend the toxic effects of alcohol and raise its blood concentration above the legal limit for driving.[2]

1. Schumock G, *et al.* Verapamil inhibits ethanol elimination. *Pharmacotherapy* 1989; 9: 184–5.
2. Anonymous. Does verapamil increase the effects of alcohol? *Pharm J* 1990; 244: 14.

Pharmacokinetics

Alcohol is rapidly absorbed from the gastrointestinal tract and is distributed throughout the body fluids. It readily crosses the placenta. Alcohol vapour can be absorbed through the lungs. Absorption through intact skin is said to be negligible.

The rate of absorption of alcohol from the gastrointestinal tract may be modified by such factors as the presence of food, the concentration of alcohol, carbonation of the alcoholic beverage, and the period of time during which it is ingested.

Alcohol is mainly metabolised in the liver; it is converted by alcohol dehydrogenase to acetaldehyde and is then further oxidised to acetate. A hepatic microsomal oxidising system is also involved. About 90 to 98% of alcohol is oxidised and the remainder is excreted unchanged by the kidneys and the lungs. It also appears in breast milk, sweat, and other secretions.

The rate of metabolism may be accelerated after repeated excessive intake and by certain substances including insulin.

Reviews.
1. Holford NHG. Clinical pharmacokinetics of ethanol. *Clin Pharmacokinet* 1987; 13: 273–92.
2. Lotsof J. A revised pharmacokinetic model for alcohol. *Clin Pharmacokinet* 2003; 42: 585–7.
3. Paton A. Alcohol in the body. *BMJ* 2005; 330: 85–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Germikill; Higiemax; Sanitizante; ***Austral.***: Aqium; Microshield Antimicrobial Hand Gel†; ***Canad.***: Alcare†; Alcoscrub†; Bactisan†; Biobase; Digisan; Duonalc-E Mild†; Hand Sanitizer; Kimcare Instant Hand Sanitizer; Lever San†; One Step Hand Sanitizer; President's Choice Hand Sanitizer; Purell; Septe FX Skin Formula†; Soft Care Instant Hand Sanitizer; Stoko Hand Sanitizer; Surgicept†; ***Chile***: Gelicol; ***Fr.***: Curethyl; Pharmadose alcool; ***Ger.***: AHD 2000; Cutasept med; Fugaten; Manusept basic; Sterillium med; Sterillium Virugard; ***Indon.***: Handy Clean; ***Israel***: Alcotint; Dr-Fischer Pharma-Gel; ***Ital.***: Sicura3 Gel; ***Malaysia***: QuickClean; ***Philipp.***: AHD 2000†; ***Thai.***: Cohol UD; ***USA***: Alcare; Bodi Line Action; Gel-Stat.

Multi-ingredient Preparations. *Arg.*: Cutidermin Crema Antibacterial†; Higienizador Manos; Omicohol A; Pervicol Toallas; Pervicol; ***Austral.***: Clean & Clear Oil Controlling Toner; Dermatech Liquid†; Microshield Handrub; Microshield Tincture; Septivon; SM-33 Adult Formula; SM-33; ***Austria***: Dodesept Gefärbt; Dodesept N†; Dodesept; Skinsept mucosa†; Skinsept; ***Belg.***: Sabenyl†; Softa Man; ***Canad.***: Anti-Bacterial Deep Cleansing; Anti-Bacterial Waterless†; Avagard CHG; Biobase-G; Biomers; Biosurf; Biotext; Duonalc-E†; Green Antiseptic Mouthwash & Gargle†; Manorapid Synergy; Purmist; Sani-Dex†; Sterigel; ***Chile***: Acnoxyl Locion Tonica; Alcolex†; Listerine; Listermint Con Fluor†; Oralfresh Citrus†; Oralfresh Clasico†; Oralfresh; Pectokast; *Cz.*: Promanum N; Softa-Man; ***Fin.***: Otiborin; ***Fr.***: Alco-Aloe†; Aniospray 29†; Clinogel Derma+; ***Ger.***: Aerodesin; Autoderm Extra; Bacillol AF; Bacillol Foam; Bacillol Tissues; Bacillol Wipes; Bacillol†; Betaseptic; Freka-Derm†; Freka-Nol†; Freka-Sept 80†; Hoffmannstropfen; Hospidermin; Hospisept; Incidin; Klosterfrau Pranzbrannrwein Latschenkiefer†; Klosterfrau Franzbranntwein Menthol†; Klosterfrau Franzbranntwein†; Klosterfrau Melissengeist; Manusept viruzid†; Mucasept-A; Promanum N; Skinsept G; Skinsept mucosa; Softa Man; Softasept N; Spirol; Spitacid; Virusept†; ***Gr.***: Faragel-Forte; Revigel; ***Hong Kong***: Duraprep†; Listerine Tartar Control; Listerine; ***India***: AM-PM Plus; AM-PM Special; Bayers Tonic; Cool Mint Listerine; Daslin; Dettol; Dettolin; Hexiprep-T; KMR; Listerine; Microgard; Neo-Cordial; Neogadine SG; Neogadine; Neurophosphates-Iron; ***Indon.***: Allerin; Benadryl CM†; Berlifed; Chlorphemin; Coricidin; Dactylen; Domeryl; Eksedryl Expectorant; Inadryl Plus; Inadryl; Koffex; Listerine Coolmint†; Listerine†; Neo Novapon; Nichodryl; Paradryl; ***Israel***: Alcosept; Alcoxidine; Salisol†; Septadine; Spirit Salicyl; V-Tabur; ***Ital.***: Bemonalcool; Citroclorex; Citromed 85; Citromed Chirurgico; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosteril Strument; Clorexan Ferri†; Eso Ferri Alcolico; Esoalcolico Incolore; Esoform Alcolico; Forbrand; Formedico; Incidin Spezial†; Incidur Spray†; Jodieci; Melsept Spray; Neomedil; Panseptil†; Sekumatic†; Simpottantacinque; Softa Man; ***Mex.***: Varicyl; ***Neth.***: Softa-Man; ***Philipp.***: BSI Medicated Spray; Dermablend Clarifying; Listerine Coolmint; Listerine Original; Zilactin; Ziladent; ***Port.***: Promanum†; Softasept; ***S. Afr.***: Clearasil Medicated Facial Cleanser†; Dry & Clear Medicated Skin Cleanser†; Listerine Antiseptic; Oxipor VHC†; Specific Nerve Pain Remedy†; ***Singapore***: Alcohol Hand Rub; Desderman; Hexodane Handrub; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; ***Spain***: Alcohocel†; Alcohol Benzalconio; Alcohol CL Benz†; Alcohol Potenciado; Alcohol Potenciado; Beta Alcanforado†; Beta Romero; Embrocacion Gras†; Farmalcohol†; Linimento Naion; Menalcol; ***Swed.***: Vitatonin†; ***Switz.***: Betaseptic; Jodoplex Teinture†; Promanum N†; Silence†; Skinsept; Softasept N; ***Thai.***: Hand Joy; ***UK***: Brushtox; Clearasil Pore Cleansing Lotion; Medi-Wipe; Oxy Cleanser; Oxy Cleanser; Oxy Duo Pads; Oxy Duo Pads; Spectrum; ***Ukr.***: Softa-Man (Софта)†; ***USA***: Banadyne-3; Clearasil Double Clear; Clearasil Double Textured Pads; Lipmagik; Maximum Strength Anbesol; Orasol; Stri-Dex Pads; Tonsiline; ***Venez.***: Prixonil.

Pharmacopoeial Preparations

USP 36: Alcohol in Dextrose Injection; Cascara Sagrada Fluidextract; Dehydrated Alcohol Injection; Rubbing Alcohol.

Alexidine *(USAN, rINN)*

Alexidina; Alexidinum; Bisguadine; Compound 904; Win-21904; Алексидин.

1,1'-Hexamethylenebis[5-(2-ethylhexyl)biguanide].

$C_{26}H_{56}N_{10}$=508.8.

CAS — 22573-93-9.

UNII — GVN71CAL3G.

Profile

Alexidine is a bisbiguanide antiseptic with properties similar to those of chlorhexidine (p. 1743.2). It is used in oral hygiene products for the treatment of inflammatory and infectious conditions including gingivitis, periodontitis, and stomatitis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Singapore*: Esemdent.

Alkyl Gallates

Galatos de alquilo; Алкилгаллаты.

Dodecyl Gallate

Dodecilo galatas; Dodécyle, gallate de; Dodecylgallat; Dodecyl-gallát; Dodecylis Gallas; Dodekyyligallaatti; E312; Galato de dodecilo; Lauryl Gallate; Laurylum Gallicum; Додецилгаллат.

Dodecyl 3,4,5-trihydroxybenzoate.

$C_{19}H_{30}O_5$=338.4

CAS — 1166-52-5.

UNII — 45612DY463.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dodecyl Gallate). A white or almost white crystalline powder. M.p. about 96 degrees. Very slightly soluble or practically insoluble in water; freely soluble in alcohol; slightly soluble in dichloromethane. Store in nonmetallic containers. Protect from light.

Ethyl Gallate

Galato de etilo; Этилгаллат.

Ethyl 3,4,5-trihydroxybenzoate.

$C_9H_{10}O_5$=198.2

CAS — 831-61-8.

UNII — 235I6UDD3L.

Pharmacopoeias. In *Br.*

BP 2014: (Ethyl Gallate). A white to creamy-white, odourless or almost odourless, crystalline powder. Slightly soluble in water; freely soluble in alcohol and in ether; practically insoluble in arachis oil. Protect from light. Avoid contact with metals.

Octil Gallate

E311; Galato de octilo; Octyl Gallate; Octyle, gallate d'; Octylgallat; Octylis gallas; Oktilo galatas; Oktylgallat; Oktyl-gallát; Oktyyligallaatti; Октилгаллат.

Octyl 3,4,5-trihydroxybenzoate.

$C_{15}H_{22}O_5$=282.3

CAS — 1034-01-1.

UNII — 079IIA2811.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Octyl Gallate). A white or almost white crystalline powder. Practically insoluble in water and in dichloromethane; freely soluble in alcohol. Store in nonmetallic containers. Protect from light.

Propyl Gallate

E310; Galato de propilo; Propil-gallát; Propilo galatas; Propyle, gallate de; Propylgallat; Propyl-gallát; Propylis gallas; Propylu galusan; Propylum Gallicum; Propyyligallaatti; Пропилгаллат.

Propyl 3,4,5-trihydroxybenzoate.

$C_{10}H_{12}O_5$=212.2

CAS — 121-79-9.

UNII — 8D4SNN7V92.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Propyl Gallate). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Propyl Gallate). A white crystalline powder with a slight characteristic odour. Slightly soluble in water; freely soluble in alcohol. Store in airtight containers. Avoid contact with metals. Protect from light.

Uses

The alkyl esters of gallic acid (3,4,5-trihydroxybenzoic acid) have antoxidant properties and are used as preservatives in pharmaceuticals and cosmetics. Alkyl gallates are also used as antoxidants in foods and are useful in preventing deterioration and rancidity of fats and oils. They are used in concentrations of 0.001 to 0.1%.

To improve acceptability and efficacy, the alkyl gallates are frequently used with other antoxidants such as butylated hydroxyanisole or butylated hydroxytoluene and with sequestrants and synergists such as citric acid and zinc salts.

The alkyl gallates have also been reported to have limited antibacterial and antifungal activity.

Adverse Effects and Precautions

The alkyl gallates may cause contact sensitivity and skin reactions.

Effects on the blood. Methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula has been reported.[1] Propyl gallate was suspected of being the most likely cause because its chemical structure is similar to pyrogallol (p. 1718.2), a methaemoglobinaemia inducer.

1. Nizzan M, *et al.* Infantile methemoglobinemia caused by food additives. *Clin Toxicol* 1979; 15: 273–80.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: He Yue (和悦); Tian Fu Chu (天复初).

Alkyldimethylethylbenzyl Ammonium Chloride

CAS — 68956-79-6 (C12-C18 alkyldimethylethylbenzyl ammonium chloride); 85409-23-0 (C12-C14 alkyldimethylethylbenzyl ammonium chloride).

Profile

Alkyldimethylethylbenzyl ammonium chloride is a quaternary ammonium compound with similar properties to benzalkonium chloride (alkyldimethylbenzyl ammonium chloride; p. 1737.1). Mixtures of alkyldimethylethylbenzyl ammonium chlorides of different alkyl chain lengths are used as disinfectants, often with benzalkonium chloride.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Advance Quat; Brillex; Cadisan; Cetainty†; Kemsol; Prevent X†.

Ambazone *(BAN, rINN)*

Ambatsoni; Ambazon; Ambazona; Ambazonum; Амбазон.

4-Amidinohydrazonocyclohexa-1,4-dien-3-one thiosemicarbazone monohydrate.

$C_8H_{11}N_5S.H_2O$=255.3

CAS — 539-21-9 (anhydrous ambazone); 6011-12-7 (ambazone monohydrate).

ATC — R02AA01.

ATC Vet — QR02AA01.

UNII — BYK4592A3Q.

Profile

Ambazone is an antiseptic that is used in the form of lozenges for minor infections of the mouth and pharynx.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Faringosept; *Rus.*: Faringosept (Фарингосепт); *Ukr.*: Faringosept (Фарингосепт).

Aminoquinuride Hydrochloride *(rINNM)*

Aminoquinuride, Chlorhydrate d'; Aminoquinuridi Hydrochloridum; Hidrocloruro de aminoquinurida; Аминохинурида Гидрохлорид.

1,3-Bis(4-amino-2-methyl-6-quinolyl)urea dihydrochloride.

$C_{21}H_{20}N_6O.2HCl$=445.3

CAS — 3811-56-1 (aminoquinuride); 5424-37-3 (aminoquinuride hydrochloride).

UNII — P2YT71SUIU.

Profile

Aminoquinuride hydrochloride is an antiseptic that has been used in topical preparations for the treatment of mouth and skin disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Herviros.

Amylmetacresol *(BAN, rINN)*

Amilmetacresol; Amilmetakrezol; Amylmétacrésol; Amylmetacresolum; Amylmetakresol; Amyylimetakresoli; Амилметакрезол.

6-Pentyl-*m*-cresol; 5-Methyl-2-pentylphenol.

$C_{12}H_{18}O$=178.3

CAS — 1300-94-3.

UNII — 05W904P57F.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Amylmetacresol). A clear or almost clear liquid or a solid crystalline mass, colourless or slightly yellow when freshly prepared; it darkens or discolours to dark yellow, brownish-yellow, or pink on keeping. F.p. about 22 degrees. Practically insoluble in water; very soluble in alcohol and in acetone. Store in non-metallic airtight containers. Protect from light.

Profile

Amylmetacresol is a phenolic antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Antiseptic Throat Drops†; Antiseptic Throat Lozenges; *UK*: Antiseptic Throat Lozenges; Throaties Anti-Bacterial Pastilles.

Multi-ingredient Preparations. *Arg.*: Strepsils Plus; Strepsils; *Austral.*: Strepsils Numbing; Strepsils Plus†; Strepsils; *Austria*: Coldangin; Neo-Angin; *Belg.*: Strepsils + Lidocaine; Strepsils Cool Mint; Strepsils Menthol†; Strepsils Vit C; Strepsils; *Canad.*: Cepacol Sensations Cooling; Cepacol Sensations Sore Throat & Blocked Nose; Cepacol Sensations Sore Throat & Cough; Cepacol Sensations Warming; Cepacol Sensations; Strepsils Cherry†; Strepsils Cool; Strepsils Sore Throat Blocked Nose; Strepsils; *Cz.*: Neo-Angin; Strepsils Cooling Mint; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; *Denm.*: Strepsils; *Fin.*: Med-Angin; Strepsils Menthol; Strepsils; *Fr.*: Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsils; Strepsilspray; *Ger.*: Dobendan Cool†; Dobendan Junior; Dobendan Synergie; Dobendan Warm; Neo-Angin; *Gr.*: Strepsils Plus; Strepsils; *Hong Kong*: Strepsils Dual Action; Strepsils; *Hung.*: Neo-Angin; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; *India*: Cof Q; Cofsils; *Irl.*: Strepsils +Plus Anaesthetic; Strepsils Cool; Strepsils Dual Action†; Strepsils Sore Throat and Blocked Nose; Strepsils Throat; Strepsils Vitamin C; Strepsils; *Israel*: Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; Strepsils; *Ital.*: Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; Benagol; *Malaysia*: Chericof; Strepsils Dual Action; Strepsils; *Neth.*: Strepsils Menthol & Eucalyptus†; Strepsils Sinaasappel & Vitamine C; Strepsils; *NZ*: Strepsils Plus Anaesthetic; Strepsils with Vitamin C; Strepsils; *Philipp.*: Strepsils; Strepsils; Therasil; *Pol.*: Neo-Angin; Strepsils; *Port.*: Benagol†; Strepsils; *Rus.*: Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс); Gorpils (ГОРПИЛС); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Strepsils with Vitamin C (Стрепсилс с Витамином С); Suprima-Lor (Суприма-Лор); Therasil (Терасил); *S. Afr.*: Strepsils Eucalyptus Menthol†; Strepsils Orange-C†; Strepsils Plus; Strepsils Soothing Honey & Lemon†; Strepsils; *Singapore*: Cofsils; Robitussin Medicated Lozenges; Strepsils Max Plus; Strepsils; *Spain*: Strepsils con Vitamina C; Strepsils Lidocaina; Strepsils; *Swed.*: Strepsils; *Switz.*: Strepsils with Vitamin C; Strepsils; *Thai.*: Strepsils Butter Menthol Capsicum†; Strepsils Maxipluzz; Strepsils Plus Vit C; Strepsils Sugar Free†; Throatsil Plus; Throatsil; *Turk.*: Med-Angin; Strepsils C; Strepsils Mentol; Strepsils; *UK*: Strepsils with Vitamin C; Strepsils; *Ukr.*: Coldact Lor Pils (Колдакт Лор Пилс); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс).

Amylphenol

p-tert-Pentylphenol; 4-t-Amylphenol.

4-(1,1-Dimethylpropyl)phenol.

$C_{11}H_{16}O$=164.2

CAS — 80-46-6.

UNII — 6NP9LYK846.

Profile

Amylphenol has been used as a phenolic disinfectant and antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: BTK-Plus†.

Ascorbyl Palmitate

Ascorbilo, palmitato de; Ascorbyle, palmitate d'; Ascorbylis palmitas; Askorbilo palmitatas; Askorbylpalmitat; Askorbylpalmitát; Askorbylu palmitynian; Askorbylylpalmitaatti; Aszkorbil-palmitát; Palmitoylascorbinsäure; Vitamin C Palmitate; Аскорбилпальмитат.

L-Ascorbic acid 6-hexadecanoate; L-Ascorbic acid 6-palmitate; 3-Oxo-L-gulofuranolactone 6-palmitate.

$C_{22}H_{38}O_7$=414.5

CAS — 137-66-6.

UNII — QN83US2B0N.

NOTE. The code E304 is used for fatty acid esters of ascorbic acid, which include ascorbyl palmitate.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Ascorbyl Palmitate). A white or yellowish-white powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol; practically insoluble in dichloromethane and in fatty oils. Store in airtight containers. Protect from light.

USNF 31: (Ascorbyl Palmitate). A white to yellowish-white powder with a characteristic odour. Very slightly soluble in water, in chloroform, in ether, and in vegetable oils; soluble 1 in 125 of alcohol. Store at 8 degrees to 15 degrees in airtight containers.

Profile

Ascorbyl palmitate is an antoxidant used as a preservative in pharmaceutical products and foods. It is often used with alpha tocopherol (p. 2119.1), and this combination shows marked synergy. As it is a fat-soluble derivative of vitamin C (ascorbic acid, p. 2110.3), ascorbyl palmitate is sometimes used as a source of vitamin C in nutritional supplements.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Chile*: Neolucid-C†.

Multi-ingredient Preparations. *Arg.*: Aminoterapia Capilar; *Hong Kong*: Proflavanol†; *Malaysia*: Proflavanol†; *Singapore*: Proflavanol†; Scar Esthetique.

Benzalkonium Chloride *(BAN, rINN)*

Benzalkoniumklorid; Bentsalkoniumkloridi; Benzalconio Cloruro; Benzalconio, cloruro de; Benzalkonii Chloridum; Benzalkonio chloridas; Benzalkoniowy chlorek; Benzalkonium Chloratum; Benzalkonium, chlorure de; Benzalkoniumchlorid; Benzalkoniumchlorid; Benzalkónium-klorid; Benzalkonyum Klorür; Cloreto de Benzalconio; Cloruro de benzalconio; Бензалкония Хлорид.

CAS — 8001-54-5.

ATC — D08AJ01; D09AA11; R02AA16.

ATC Vet — QD08AJ01; QD09AA11; QR02AA16.

UNII — F5UM2KM3W7.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.* Some pharmacopoeias also have a monograph for a solution.

Chin. also includes benzalkonium bromide.

Ph. Eur. 8: (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides, the alkyl groups mainly having chain lengths of C_{12}, C_{14}, and C_{16}. It contains not less than 95% and not more than 104% of alkylbenzyldimethylammonium chlorides, calculated as $C_{22}H_{40}ClN$ with reference to the anhydrous substance.

A white or yellowish-white powder, or gelatinous, yellowish-white hygroscopic fragments. It forms a clear molten mass on heating. It contains not more than 10% of water. Very soluble in water and in alcohol. An aqueous solution froths copiously when shaken.

USNF 31: (Benzalkonium Chloride). A mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5.CH_2.N(CH_3)_2.R]Cl$, in which R represents a mixture of the alkyls having chain lengths from C_8 to C_{16}. It contains not less than 40% of the $C_{12}H_{25}$ compound, calculated on the anhydrous substance, not less than 20% of the $C_{14}H_{29}$ compound, and not less than 70% of the 2 compounds together.

A white or yellowish-white, thick gel, or gelatinous pieces with a mild aromatic odour. It contains not more than 15% of water. Very soluble in water and in alcohol; the anhydrous form is soluble 1 in 100 of ether and 1 in 6 of benzene. A solution in water is usually slightly alkaline and foams strongly when shaken. Store in airtight containers.

Incompatibility. Benzalkonium chloride is incompatible with soaps and other anionic surfactants, citrates, iodides, nitrates, permanganates, salicylates, silver salts, tartrates, and zinc oxide and sulfate. Incompatibilities have been noted with ingredients of some commercial rubber mixes or plastics. Incompatibilities have also been reported with other substances including aluminium, cotton dressings, fluorescein sodium, hydrogen peroxide, hypromellose, kaolin, hydrous wool fat, and some sulfonamides.

Uses and Administration

Benzalkonium chloride is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of the other cationic surfactants (see Cetrimide, p. 1742.1). It is also used as an antimicrobial preservative for pharmaceutical products. Benzalkonium bromide and benzalkonium saccharinate have also been used.

Solutions of benzalkonium chloride 0.01 to 0.1% are used for cleansing skin, mucous membranes, and wounds. More dilute solutions of 0.005% are suitable for irrigation of deep wounds. A 0.02 to 0.05% solution has been used as a vaginal douche. An aqueous solution containing 0.005 to 0.02% has been used for irrigation of the bladder and urethra and a 0.0025 to 0.005% solution for retention lavage of the bladder.

Creams containing benzalkonium chloride are used in the treatment of napkin rash and other dermatoses.

A 0.2 to 0.5% solution has been used as a shampoo in seborrhoeic dermatitis.

Lozenges containing benzalkonium chloride are used for the treatment of superficial infections of the mouth and throat.

Benzalkonium chloride is used as a preservative in ophthalmic solutions at a concentration of 0.01 to 0.02%, and in nasal and otic solutions at a concentration of 0.002 to 0.02%. Benzalkonium chloride is used for disinfecting rigid contact lenses (p. 1730.2) but is unsuitable as a preservative in solutions for washing and storing hydrophilic soft contact lenses (see also Effects on the Eyes, below).

Benzalkonium chloride is also used as a spermicide.

Solutions of 0.13% have been used for disinfection and storage of surgical instruments, sometimes with the addition of sodium nitrite to inhibit rust.

Action. The antibacterial effect of benzalkonium chloride 0.003% was enhanced by 0.175% of benzyl alcohol, phenylpropanol, or phenethyl alcohol.[1] For the use of phenethyl alcohol with benzalkonium chloride as a preservative for ophthalmic solutions, see Antimicrobial Action, under Phenethyl Alcohol, p. 1763.2.

1. Richards RME, McBride RJ. Enhancement of benzalkonium chloride and chlorhexidine acetate activity against Pseudomonas aeruginosa by aromatic alcohols. *J Pharm Sci* 1973; 62: 2035–7.

Catheter-related sepsis. Benzalkonium chloride has been investigated[1,2] for incorporation into catheters to reduce catheter-related sepsis (p. 1732.1).

1. Tebbs SE, Elliott TSJ. A novel, antimicrobial central venous catheter impregnated with benzalkonium chloride. *J Antimicrob Chemother* 1993; 31: 261–71.
2. Moss HA, *et al.* A central venous catheter coated with benzalkonium chloride for the prevention of catheter-related microbial colonization. *Eur J Anaesthesiol* 2000; 17: 680–7.

Adverse Effects, Treatment, and Precautions

As for Cetrimide, p. 1742.2. Because some rubbers are incompatible with benzalkonium chloride silicone rubber teats should be used on eye drop containers unless the suitability has been established.

Catheters and cannulas. For reference to benzalkonium chloride used in the manufacturing process of heparin-bonded catheters interfering with determination of serum concentrations of sodium and potassium, see under Precautions for Heparin, p. 1400.1.

Effects on the eyes. Benzalkonium chloride is one of the most disruptive ophthalmic additives to the stability of the lipid film and to corneal epithelial membranes.[1] Toxicity studies have tended to be carried out using relatively high concentrations of benzalkonium chloride.[2] However, damage to the tear film and corneoconjunctival surface and various forms of conjunctivitis have been reported in patients receiving regular long-term treatment for glaucoma with eye drops preserved with benzalkonium chloride in usual concentrations.[3-6]

Corneal toxicity[7] (with long-term recovery[8]) has also been reported in patients inadvertently exposed to benzalkonium chloride as a preservative in viscoelastic material during cataract surgery. The use of preservatives in eye drops should generally be avoided and the formulation of such preparations in single-dose containers is desirable.[1,2] Benzalkonium chloride is not suitable for use in solutions for storing and washing hydrophilic soft contact lenses, as it can bind to the lenses and may later produce ocular toxicity when the lenses are worn.[9] Similarly, benzalkonium chloride use in anaesthetic eye drops is discouraged, as the anaesthetic component reduces the blink reflex and increases the contact time with the eye drops which may consequently result in increased toxicity due to the preservative. Patients with dry eye syndrome are also at increased risk of toxicity as the corneal epithelium is exposed to the full strength of the eye drops, in addition to which these patients do not produce enough tears to dilute the preservative in the eye drops.

1. Burstein NL. The effects of topical drugs and preservatives on the tears and corneal epithelium in dry eye. *Trans Ophthalmol Soc U K* 1985; 104: 402–9.
2. Burstein NL. Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 1980; 25: 15–30.
3. Herreras JM, *et al.* Ocular surface alteration after long-term treatment with an antiglaucomatous drug. *Ophthalmology* 1992; 99: 1082–8.
4. Kuppens EVMJ, *et al.* Effect of timolol with and without preservative on the basal tear turnover in glaucoma. *Br J Ophthalmol* 1995; 79: 339–42.
5. Gibran SK. Unilateral drug-induced ocular pseudopemphigoid. *Eye* 2004; 18: 1270.
6. Kahana A, *et al.* Drug-induced cicatrising granulomatous conjunctivitis. *Br J Ophthalmol* 2007; 91: 691–2.
7. Eleftheriadis H, *et al.* Corneal toxicity secondary to inadvertent use of benzalkonium chloride preserved viscoelastic material in cataract surgery. *Br J Ophthalmol* 2002; 86: 299–305.
8. Hughes EH, *et al.* Long-term recovery of the human corneal endothelium after toxic injury by benzalkonium chloride. *Br J Ophthalmol* 2007; 91: 1460–3.
9. Gasset AR. Benzalkonium chloride toxicity to the human cornea. *Am J Ophthalmol* 1977; 84: 169–71.

Effects on the respiratory tract. Hypersensitivity to benzalkonium chloride, used as a preservative in nasal drops, was confirmed in a patient by a challenge that produced nasal congestion and irritation of the eyes and throat lasting 48 hours.[1] A review[2] of 18 studies (14 *in vivo*, 4 *in vitro*) where benzalkonium chloride was used as the preservative in multidose nasal products found that 8 studies (all *in vivo*) found no toxic effects, while 10 reported degenerative changes to the nasal epithelia or exacerbation of rhinitis medicamentosa. However, in only 2 of these 10 studies were the differences between benzalkonium chloride and control groups found to be significant, and both of these included the use of oxymetazoline, which is known to cause rhinitis medicamentosa.

Benzalkonium chloride used as a preservative in nebulised solutions of anti-asthma drugs has been reported to cause dose-related bronchoconstriction especially in asthmatic patients,[3] and has been associated with the precipitation of respiratory arrest.[4]

1. Hillerdal G. Adverse reaction to locally applied preservatives in nose drops. *ORL J Otorhinolaryngol Relat Spec* 1985; 47: 278–9.
2. Marple B, *et al.* Safety review of benzalkonium chloride used as a preservative in intranasal solutions: an overview of conflicting data and opinions. *Otolaryngol Head Neck Surg* 2004; 130: 131–41.
3. Committee on Drugs, American Academy of Pediatrics. "Inactive" ingredients in pharmaceutical products: update. *Pediatrics* 1997; 99: 268–78.
4. Boucher M, *et al.* Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother* 1992; 26: 772–4.

Interactions

Benzalkonium chloride is not suitable for use in eye drops containing local anaesthetics (see Effects on the Eyes, above).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hidratant; Pharmatex; *Austral.*: Dettol Fresh; *Belg.*: Cedium; Dettol†; *Braz.*: Fluimucil Solucao Nasal; *Canad.*: Anti-Microbe; Antiseptic Swabs; Ato Quat; Bac Liq; Bac-Killer; Bactocide; Bactol; Dermaguard†; Digisan E; Eco-Clean Elite†; Ecocare 360; Germiphene; Handclens; Hands Fresh; Hands On Antiseptic; Hands2Go; Hydra Bain/Bath†; Kid's Hand Gel; Loris BZK; Micro Clear; One Step Foaming Antiseptic Wash; One Step Foaming Hand Sanitizer; Ready Bath; Rinse-Free; Sani Hands AF; Soapopular; Soft T Cleanse†; Sting Stop; Swabplus Antiseptic†; Thuroclens; *Chile*: Germosept; *China*: Bang-Aid (邦迪); *Cz.*: Dettol; Pharmatex; *Fr.*: Dettolpro; Humex Fournier; Pharmatex; *Ger.*: Killavon; Laudamonium; Mikrobac basic; *Hong Kong*: Pharmatex; *Hung.*: Pharmatex; *India*: Iteol-H; *Irl.*: Dettol Fresh†; Pharmatex; Preventex; *Ital.*: Alfa C; Benalcon; Bergagyn; Bluesteril†; Citrosil; Citrosteril Ambiente; Citrosteril Deterferri; Detergil; DiMill; Diseptil†; Disigien; Disintyl; Display; Distasil†; Disteril; Eso Deterferri; Eso Ferri; Esosan Casa; Esosan Soap; Germicidin†; Germozero; Helis†; Hygienist Pavimenti e Piastrelle; Iridina Light; Lacribase; Lozione Vittoria; Maxisteril†; Neo-Desogen; Polisan†; Sanaform; SaniSteril Deterferri; Saquat†; Sguardi; Steramina G; Stilla Delicato; Ten-Quat; Video-Light; *Mex.*: Derman Talco; *Neth.*: Dettol med benzalkoniumchloride; *NZ*: Dettol Fresh†; Dettol†; Virasolve; *Port.*: Pharmatex†; *Rus.*: Benatex (Бенатекс); Farmaginax (Фармагинэкс); Gynecotex (Гинекотекс); Kontratex (Контратекс); Pharmatex (Фарматекс); Spermatex (Спематекс); *Spain*: Crema Contraceptiva Lanzas; Dettolmed; Mini Ovulo Lanzas†; *Swed.*: Dettolmed; *Thal.*: Pose-Bac†; *Turk.*: Zefan; Zefiran; Zefirolum; Zefol; Zefort†; Zefsolin; Zenfektol†; Zentan†; *UK*: Bradosol; Dermax Therapeutic Shampoo; Dettol Antiseptic Wash; Dettol Fresh; *Ukr.*: Erotex (Эротекс); Pharmatex (Фарматекс); Virotek Intim (Виротек Интим); *USA*: Bacti-Cleanse; Benza; Remedy; Zephiran; *Venez.*: Decomed.

Multi-ingredient Preparations. *Arg.*: Antiseptic Plus†; Collubiazol N; Crema de Ordene; Eurocoal; Gripace; Hexil Antiseptico; Merthiolate Anestesico; Merthiolate Nueva Formula; Muelita; Neo Coltirot; Polviderm NF; Soquette†; *Austral.*: Animine†; Animine; Clean Skin Face Wash†; Mycil Healthy Feet; Oilatum Plus; Paxyl; QV Flare Up; Virasolve; *Austria*: Dequonal; Dorithricin; Limexx†; Tyrothricin comp; *Belg.*: Akinspray†; *Braz.*: Belagin†; Colpist; Colpistar; Colpistatin; Dinill; Donnagel; Drapolene; Ginestatin†; Higicler; Kolpitrat; Kuramed; Limpele Ginecologico; Nasolin; Oxizinco†; Pomada Minancora; Soronal; Tricomax; Vagi Biotic; Visolon; *Canad.*: Advance Quat; Anti-Bacterial Waterless†; Aseptone Quat; Avon Footworks Cracked Heel†; Bactine; Bio Klean; Brillex; Cadisan; Cetainty†; Dr Scholl's Cracked Heel Relief†; Family Medic First Aid Treatment; Kemsol; Medi-Dan; Prevent X†; Tanac; *Chile*: Dermobarrina; Dexagin; *China*: Drapolene (保芙); *Cz.*: Coldrex Proti Bolesti v Krku; Oilatum Plus; Septolete; *Fr.*: Biseptine; Dermaspraid Antiseptique†; Dermobacter; Euvanol; Humex Mal de Gorge; Kenalcol†; Mercryl; Mercrylsoins; Mercrylspray; Rhinofluimucil; *Ger.*: Cutasept; Dequonal; Dorithricin; Dynexan Mundgel; Freka-Derm†; Freka-Sept 80†; Gingicain D; Hexaquart S; Incidin extra N; Incidin perfekt; Incidin; Kohrsolin FF; Korsolex Extra; Korsolex FF; Mikrobac Tissues; Mikrobac; Sekusept Extra N; Skinman Soft; Ultrasol-F; *Gr.*: Beta Opthiole; Cutasept; Derma; Olamyc; *Hong Kong*: Dequasin; Dermobacter; Dermojela; Mycil†; Oilatum Plus; Oris-gel†; Protectaid; *Hung.*: Dorithricin; Septolete; *India*: Bonzela; Dentogel; Dologel-CT; Pairgenol-H; Happynap; Nitra-Dent; Oilatum Plus; Orex; Rash-free; *Indon.*: Mexochrome†; Oilatum Plus†; *Irl.*: Drapolene; Emulsiderm; Mycil; Oilatum Junior Flare-Up; Oilatum Plus; Torbetol†; *Israel*: Aphtagone†; Aptha-X†; Claritone; Emulsiderm; Protectaid; *Ital.*: AZ 15; Barrycidal; Bemonalcool; Cerosteril; Citrocil Alcolico†; Citromed 85; Citromed Chirurgico; Citromedics Pronto†; Citrosil Alcolico Azzuro; Citrosil Alcolico Bruno; Citrosil Alcolico Incolore; Citrosil Nubesan; Citrosteril Impronte; Citrosteril Pronto; Citrosteril Strumenti; Eso Ferri Alcolico; Eso S 80; Esoalcolico Incolore; Esoform 92; Esoform Alcolico; Esosan Pronto; Germozero Dermo; Incidin Spezial†; Incidur Spray†; Indulfan†; Linea F; Neo Emocicatrol; Neomedil; Norica Plus; Odongi; Pupilla Light; Rexichlor; Sangen Casa; Sangen Casa; Sicura3 Medical; Simp; Simpottantacinque; Sterosan; Tirs; Zincometil; *Malaysia*: Drapolene; Oilatum Plus Antibacterial; QV Flare Up†; *Mex.*: Dermacid; Glossderm; Novageon; *NZ*: Oilatum Plus; *Philipp.*: Drapolene; Oilatum Plus; *Pol.*: Cholisept Intensive; Coldrex†; Oilatum Plus; Septolete; *Rus.*: Bactoderm (Бактодерм); Dologel (Дологель); Drapolene (Драполен); Septogal (Септоган); Septolete (Септолете); *S.Afr.*: Oilatum Plus; *Singapore*: Dorithricin; Drapolene; Napitol; Oilatum Plus; QV Flare Up; *Spain*: Aftajuventus; Alcohol Benzalconio; Alcohol CL Benz†; Alcohol Potenciado; Avril; Dermo H Infantil†; Desinvag†; Ginejuvent; Lindemil; Odamida; Otogen Calmante; Phonal; Resorborina; Sebumselen; Tulgrasum Cicatrizante; Vaselatum; *Switz.*: Cutasept; Dequonal; Dettol; No Pic; Parapic†; *Thai.*: Drapolene; Gynecon-T; Gynecon; Gynoco†; Gynova†; Gyonep; Gyracon; Napilene; Nystin; Oilatum Plus†; VG Med; *Turk.*: Drapolene†; Kortos; *UK*: Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus; Boots Mouth Ulcer Pastilles; Cetanorm; Conotrane; Dermol; Dettol; Drapolene; Emulsiderm; Iglu; Mycil; Neo Baby Cream; Oilatum Plus; Protectaid; *Ukr.*: Drapolen (Драполен); Inflarax (Инфларакс); Septolete (Септолете); *USA*: Bactine Antiseptic; Bactine Pain Relieving Cleansing; Cetylcide II; Cortic ND; Medi-First with Lidocaine; Medi-Quik; Mediotic-HC; Orajel Mouth Aid; Oxyzal; Pedi-Pro; Tanac Dual Core; Tanac; Tanac; Vagi-Gard Medicated Cream; Vi Rid-Ready; Zonite; *Venez.*: Pedi-Lotion; Pedi-Lotion.

Pharmacopoeial Preparations
USNF 31: Benzalkonium Chloride Solution.

Benzethonium Chloride *(BAN, rINN)*

Bencetonio, cloruro de; Bensetoniumklorid; Bentsetoniumklorid; Benzethonii Chloridum; Benzéthonium, chlorure de; Benzethoniumchlorid; Benzethonium-chlorid; Benzetonio cloruras; Benzetoniowy chlorek; Benzetónium-klorid; Cloruro de bencetonio; Diisobutylphenoxyethoxyethyldimethylbenzylammonium chloride; Бензетония Хлорид.

Benzyldimethyl[2-[2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethoxy]ethyl]ammonium chloride.

$C_{27}H_{42}ClNO_2$=448.1

CAS — 121-54-0.

ATC — D08AJ08; R02AA09.

ATC Vet — QD08AJ08; QR02AA09.

UNII — PH41D05744.

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Benzethonium Chloride). A white or yellowish-white powder. Very soluble in water and in alcohol; freely soluble in dichloromethane. An aqueous solution froths copiously when shaken. Protect from light.

USP 36: (Benzethonium Chloride). White crystals with a mild odour. Soluble 1 in less than 1 of water, of alcohol, and of chloroform, and 1 in 6000 of ether. A 1% solution in water is slightly alkaline to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzethonium chloride is incompatible with soaps and other anionic surfactants.

Profile

Benzethonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used as a preservative in pharmaceutical and cosmetic products. It has also been used as a vaginal spermicide.

Benzethonium chloride, which produced mild skin irritation at a concentration of 5% but not lower, was not considered to be a sensitiser, and was considered to be safe at a concentration of 0.5% in cosmetics applied to the skin and at a maximum concentration of 0.02% in cosmetics used in the eye area.[1]

1. **The Expert Panel of the American College of Toxicology. Final report on the safety assessment of benzethonium chloride and methylbenzethonium chloride.** *J Am Coll Toxicol* 1985; 4: 65–106.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Avon Clearskin Invigorating Cleansing†; Clearskin Antibacterial†; Foamy Sanz; Gentle Fresh Sanitizer; Hand Sanitizer; Instant Hand Sanitizer; Kleen-San; Peri-Wash II; Sproam; Winning Hands Hand Sanitizer; Zep Foam San; *Gr.*: Pan-Vasin†; *Hong Kong*: Peri-Wash II†; *S.Afr.*: Johnson's Antiseptic Powder†; *USA*: Antiseptic Wound & Skin Cleanser.

Multi-ingredient Preparations. *Arg.*: Butimerin; Fil Olor; Gargadrin-R; Solumerin; Vagicural; *Belg.*: Neo-Golaseptine; *Braz.*: Andolba; Antimais Septico; Antiseptico Hertz†; Hipodex; Salvelox; Spray Anti-Septico; *Canad.*: Lanacane Anti-Bacterial First Aid; Lipsorex Plus; Lipsorex; Marcorodex; *Chile*: Aucusik; Lerfimin; Molca; *Ger.*: Brand- u. Wundgel-Medice; *Ital.*: Barrycidal; Sangen Casa; *NZ*: VoSoL; *S.Afr.*: Dry & Clear Medicated Skin Cleanser†; *Spain*: Alcohol Potenciado; Eupnol; Halibut; *Switz.*: Angidine†; Cemaquin†; Rhinocure simplex; Rhinocure; Tyrothricine + Gramicidine†; Undex†; *Thai.*: Iwazin; Jawkepta; Sigatricin†; Tonsilon; *USA*: Acetasol HC; Acetasol; Calagel; Dermoplast Antibacterial; Gold Bond Antiseptic First Aid Quick Spray; Skin Shield; StaphAseptic; Tecnu First Aid; Vagisil; VoSoL HC.

Pharmacopoeial Preparations
USP 36: Benzethonium Chloride Concentrate; Benzethonium Chloride Tincture; Benzethonium Chloride Topical Solution.

Benzoates

Benzoatos; Бензоаты.

Benzoic Acid

Acide benzoïque; Acidum benzoicum; Bensoesyra; Bentsoehappo; Benzoesäure; Benzoesav; Benzoico, ácido; Benzoinė rūgštis; Dracylic Acid; E210; Kwas benzoesowy; Kyselina benzoová; Бензойная Кислота.

$C_6H_5CO_2H$=122.1

CAS — 65-85-0.

UNII — 8SKN0B0MIM.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Benzoic Acid). A white or almost white, crystalline powder or colourless crystals, odourless or with a very slight characteristic odour. Slightly soluble in water; soluble in boiling water; freely soluble in alcohol and in fatty oils. M.p. 121 degrees to 124 degrees.

USP 36: (Benzoic Acid). White crystals, scales, or needles, with a slight characteristic odour. Soluble 1 in 300 of water, 1 in 3 of alcohol, 1 in 5 of chloroform, and 1 in 3 of ether; freely volatile in steam. Congealing range 121 degrees to 123 degrees.

Incompatibility. The incompatibilities of benzoic acid are described under Sodium Benzoate, below.

Sodium Benzoate

Benzoan sodný; Benzoato sódico; E211; Natrii Benzoas; Natrio benzoatas; Natrium Benzoicum; Natriumbensoat; Natriumbentsoaatti; Natriumbenzoat; Natrium-benzoát; Sodii Benzoas; Sodium, benzoate de; Sodu benzoesan; Sodyum Benzoat; Бензоат Натрия.

$C_6H_5CO_2Na$=144.1

CAS — 532-32-1.

UNII — OJ245FE5EU.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *Viet.* Also in *USNF*.

Ph. Eur. 8: (Sodium Benzoate). A white or almost white, slightly hygroscopic, crystalline or granular powder or flakes. Freely soluble in water; sparingly soluble in alcohol (90% v/v).

USNF 31: (Sodium Benzoate). A white, odourless or practically odourless, granular or crystalline powder. Soluble 1 in 2 of water, 1 in 75 of alcohol, and 1 in 50 of alcohol 90%.

Incompatibility. Benzoic acid and its salts are incompatible with quaternary compounds, calcium salts, ferric salts, and salts of heavy metals. Their activity is also diminished by nonionic surfactants or due to absorption by kaolin. They are relatively inactive above a pH of about 5.

Uses and Administration

Benzoates have antibacterial and antifungal properties. Their antimicrobial activity is due to the undissociated benzoic acid and is therefore pH-dependent. They are relatively inactive above a pH of about 5.

Benzoates are used as preservatives in pharmaceutical formulations including oral preparations; benzoic acid and sodium benzoate are typically used in concentrations of up to 0.2% and 0.5%, respectively. They are used as preservatives in foods, (and are also present naturally in some foods), and at similar concentrations in cosmetics.

Benzoic acid 6% with salicylic acid 3%, as Compound Benzoic Acid Ointment (BP 2014) (Whitfield's Ointment) has a long history of use as an antifungal (see Skin Infections, p. 568.1). Benzoic acid has also been used in desloughing preparations and has been given as a urinary antiseptic.

An injection of caffeine and sodium benzoate has been used as a CNS stimulant, but see Neonates, under Adverse Effects and Precautions, p. 1739.1 for a caution against its use in neonates.

Sodium benzoate is used as part of the treatment of hyperammonaemia that occurs in inborn errors of the urea cycle. It has also been reported to be effective in reducing plasma-glycine concentrations in nonketotic hyperglycinaemia (p. 2623.2), although it may not be effective in preventing mental retardation.

Sodium benzoate is a common ingredient of cough preparations.

Hyperammonaemia. Sodium benzoate is used for treatment of hyperammonaemia (p. 2049.3).[1–4] It is given with sodium phenylacetate (see p. 2619.2 for doses) and a combined preparation is available in some countries.

1. **Maestri NE, *et al.* Long-term survival of patients with argininosuccinate synthetase deficiency.** *J Pediatr* 1995; 127: 929–35.
2. **Maestri NE, *et al.* Long-term treatment of girls with ornithine transcarbamylase deficiency.** *N Engl J Med* 1996; 335: 855–9.
3. **Zammarchi E, *et al.* Neonatal onset of hyperornithinemia-hyperammonemia-homocitrullinuria syndrome with favorable outcome.** *J Pediatr* 1997; 131: 440–3.
4. **Enns GM, *et al.* Survival after treatment with phenylacetate and benzoate for urea-cycle disorders.** *N Engl J Med* 2007; 356: 2282–92.

Adverse Effects and Precautions

The benzoates can cause hypersensitivity reactions, but there have also been reports of non-immunological contact urticaria. The acid can be irritant to skin, eyes, and mucous membranes.

Infants given large doses of sodium benzoate have suffered vomiting. Symptoms of overdosage reported in this group have included vomiting, irritability and, in more severe cases, renal tubular dysfunction, hypokalaemia, hypocalcaemia, and metabolic acidosis.

Premature infants have been reported to be at risk of metabolic acidosis and kernicterus.

Hypersensitivity. Respiratory reactions to benzoates may occur, especially in patients susceptible to aspirin-induced asthma.[1,2] Urticarial reactions have also been associated with these compounds,[3,4] though at a lower incidence[5] and they can be non-immunological.[6] However, these reports have to be balanced against a controlled study[7] that showed no difference in the incidence of urticaria or atopic symptoms between patients given benzoic acid and those given lactose placebo. A retrospective study[8] of 47 patients who had previously shown a hypersensitivity reaction after ingesting food or products containing benzoate sodium found that the incidence of a repeat episode of acute urticaria or angioedema on re-challenge was very low (2%).

Anaphylactoid reactions have been reported in 2 patients.[9,10]

Erythema multiforme has occurred in several patients.[11]

1. **Rosenhall L. Evaluation of intolerance to analgesics, preservatives and food colorants with challenge tests.** *Eur J Respir Dis* 1982; 63: 410–19.
2. **Settipane GA. Aspirin and allergic diseases: a review.** *Am J Med* 1983; 74 (suppl): 102–9.
3. **Michaëlsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs.** *Br J Dermatol* 1973; 88: 525–32.
4. **Warin RP, Smith RJ. Challenge test battery in chronic urticaria.** *Br J Dermatol* 1976; 94: 401–6.
5. **Wüthrich B, Fabro L. Acetylsalicylsäure-und lebensmitteladditiva-intoleranz bei urtikaria, asthma bronchiale und chronischer rhinopathie.** *Schweiz Med Wochenschr* 1981; III: 1445–50.
6. **Nethercott JR, *et al.* Airborne contact urticaria due to sodium benzoate in a pharmaceutical manufacturing plant.** *J Occup Med* 1984; 26: 734–6.

7. Lahti A, Hannuksela M. Is Benzoic acid really harmful in cases of atopy and urticaria? *Lancet* 1981; ii: 1055.
8. Nettis E, *et al.* Sodium benzoate-induced repeated episodes of acute urticaria/angio-oedema: randomized controlled trial. *Br J Dermatol* 2004; 151: 898–902.
9. Moneret-Vautrin DA, *et al.* Anaphylactoid reaction to general anaesthesia: a case of intolerance to sodium benzoate. *Anaesth Intensive Care* 1982; 10: 156–7.
10. Michils A, *et al.* Anaphylaxis with sodium benzoate. *Lancet* 1991; 337: 1424–5.
11. Lewis MAO, *et al.* Recurrent erythema multiforme: a possible role of foodstuffs. *Br Dent J* 1989; 166: 371–3.

Neonates. Serious metabolic disturbances in premature neonates given intravenous fluids with benzyl alcohol as a preservative have been attributed to the accumulation of benzoic acid, a metabolite of benzyl alcohol (see p. 1740.1). This risk led to the recommendation that Caffeine and Sodium Benzoate Injection (USP), which has been given as a respiratory stimulant, should not be used in neonates.[1]

Sodium benzoate has been tried in the treatment of some neonatal metabolic disorders (see Uses and Administration, p. 1738.3). However, benzoates can also displace bound bilirubin from albumin putting neonates at risk of kernicterus.[2] Three cases of toxicity have been reported after accidental high doses of intravenous sodium benzoate and sodium phenylacetate were given to children with hyperammonaemia.[3] All the children initially became agitated and confused, had Küssmaul respiration (rapid, deep breathing) and developed a partial metabolic acidosis with an increased anion gap. Two patients subsequently developed cerebral oedema and hypotension and died while the third survived after haemodialysis.

1. Edwards RC, Voegeli CJ. Inadvisability of using caffeine and sodium benzoate in neonates. *Am J Hosp Pharm* 1984; 41: 658.
2. Schiff D, *et al.* Fixed drug combinations and the displacement of bilirubin from albumin. *Pediatrics* 1971; 48: 139–41.
3. Praphanphoj V, *et al.* Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia. *J Inherit Metab Dis* 2000; 23: 129–36.

Pharmacokinetics

The benzoates are absorbed from the gastrointestinal tract and conjugated with glycine in the liver to form hippuric acid, which is rapidly excreted in the urine.

Neonates. References.

1. Green TP, *et al.* Disposition of sodium benzoate in newborn infants with hyperammonemia. *J Pediatr* 1983; 102: 785–90.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *China*: Fu Tai (芙泰); *Gr.*: Amzoate; *Indon.*: Topix†; Yodsaben†; *Spain*: Pastillas Dr Andreu.

Multi-ingredient Preparations. *Arg.*: Expectosan Hierbas y Miel; Fungicida; Ixana; Ixana; No-Tos Adultos; No-Tos Infantil; No-Tos Infantil; Pectobron; Refenax Jarabe; *Austral.*: Whitfields (Benzoic Acid Compound) Ointment; *Austria*: Acerbine; Mycopol; *Belg.*: Pholco-Mereprine; Toplexil; *Braz.*: Bronquidex; Bronquiogen†; Dermicon; Eaca Balsamico; Expec; Frenotosse; Fungolab†; Iodesin; KI-Expectorante; Micotiazol; Penetro; Po Antisseptico†; Toplexil; *Canad.*: Bronco Asmol†; Larynsol†; Plax†; *Chile*: Broncodeina; Caristop; Diencil; Fluorencil; Gruben; Listerine; Pectoral Pasteur; Pulmagol; *China*: Bi Zhi Ke (比之可); *Denm.*: Pectyl; *Fr.*: Broncalene Nourisson†; Broncalene; Dinacode avec codeine; Ephydion†; Neo-Codion; Neo-Codion; Ozothine†; Paregorique†; Passedyl; Pastiserol†; Pate Suisse†; Pneumaseptic†; Pulmofluide Simple; Pulmosodyl; Rhinamide; *Ger.*: Gero H3 Aslan†; *Hong Kong*: Gly Thymol; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; *Hung.*: Aknesol; Glycosept; Shilajit; *India*: AM-PM Junior; AM-PM Plus; AM-PM Special; Colowash; Cool Mint Listerine; Elixir Efelin; Exomega; Exsora; Keralin; Listerine; Mycoderm; Pragmatar; Zoderm; *Indon.*: Kalpanax; Kopamex†; Listerine Coolmint†; Mikorex†; Sapona†; *Irl.*: Hemocane; Whitfield's Antifungal; *Israel*: Oxacatin; Pertussol; Phytoderm Compositum; Pitrisan†; Pitrisol; Spirit Whitfield; To-Care; Tucare; Tussophedrine NF; *Ital.*: Dentinale; Neo Borocillina Ant Oro; Neo Borocillina; Paracodina; Sedocalcio; Tiocosol†; *Malaysia*: Nixoderm; *Mex.*: Pulmovital; *Mon.*: Glyco-Thymoline; *NZ*: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; *Philipp.*: Dermalin†; Listerine Coolmint; Listerine Freshburst; Listerine Original; Listerine Teeth & Gum Defense; United Home Whitfield's Ointment; *Pol.*: Gargarin; *Port.*: Broncodiazina†; Codol; Drenoflux; Micaveen†; *Rus.*: Amtersol (Амтерсол); Mixture Conta Tussis for Adults (Микстура От Кашля Для Взрослых); Mosoile (Мозойл); Neo-Codion Babies (Нео-Кодион Для Младенцев)†; *S.Afr.*: Aserbine; Dry & Clear Medicated Skin Cleanser†; *Singapore*: Centa Skin; ETD; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; Nixoderm; Poly-N; Robinson Ringworm & Whitespot; Veelanz's Ointment; *Spain*: Acerbiol†; Broncoformo Muco Dexa†; Bronquidiazina CR; Etermol Antitusivo†; Pastillas Pectorales Kely†; Pazbronquial; Pulmofasa; Tos Mai; *Switz.*: Nican†; Onguent aux herbes Keller; Pastilles pectorales du Dr. Welti; Phol-Tux; *Thai.*: Benzo; Skin Soln; *Turk.*: Artu; Fenasthma; Fenastma; Gayabeksin; Latusin†; Nesgarin; *UK*: Eczema Ointment; Hemocane; Potters Gees Linctus; Sanderson's Throat Specific; Toepedo; *Ukr.*: Acerbin (Ацербин); Extratherm (Экстратерм); Tos-Mai (Тос-Май); *USA*: Ammonul; Atrosept; Bensal HP; Cystex; Hyophen; MHP-A; Prosed/DS; UAA; Ucephan†; Uriseptic; Uritact; *Venez.*: Acetoben; Amodion; Dromil Sauco; Niosilin; Photoderm AKN; Pi-Fedrin; Tabonuco; Yerba Santa.

Homoeopathic Preparations. *Austral.*: Elimitona Slim & Detox; Elimitona; *Austria*: Globuli gegen Gelenkschmerzen; *Canad.*: Arnica-Heel Comp†; Arthritic Pain; Backache with Arnica†; Bladder Irritation; Comp-Drops 8 Uri-Tract†; Homeo-Form AR†; Hyalgesic LBP†; Male +; Renelix; *Chile*: Arnica Compuesta; Artroplex; *Fr.*: Arthro-Drainol; Boripharm No 23; Hepatocynesine†; L 8; Ledum Complexe No 81; Natrum Carbonicum Complexe No 10†; Rhus Toxicodendron Compose; Rubia Complexe No 3; Urtica Complexe No 82†; *Ger.*: Arthrorell N; Girheulit HM†; Girheulit HOM; Hevertnier Complex N†; Hewerheum N†; Levisticum S; Rheucostan R; *Neth.*: Akutur spag; *Switz.*: Akutur; Regenaplex Nr. 21e; Regenaplex Nr. 31b.

Pharmacopoeial Preparations

BP 2014: Benzoic Acid Solution; Compound Benzoic Acid Ointment; Tolu-flavour Solution;

USP 36: Benzoic and Salicylic Acids Ointment; Caffeine and Sodium Benzoate Injection.

Benzododecinium Bromide

Benzododecinio, bromuro de; Бензододециния Бромид.

Benzyldodecyldimethylammonium bromide.

$C_{21}H_{38}BrN$=384.4

CAS — 10328-35-5 (benzododecinium); 7281-04-1 (benzododecinium bromide).

ATC — D09AA05.

ATC Vet — QD09AA05.

UNII — IRY12B27Q6.

Pharmacopoeias. In *Fr.*

Benzododecinium Chloride *(rINN)*

Benzododecinii Chloridum; Benzododecinio, cloruro de; Benzododécinium, Chlorure de; Cloruro de benzododecinio; Lauralkonium Chloride; Бензододециния Хлорид.

Benzyldodecyldimethylammonium chloride.

$C_{21}H_{38}ClN$=340.0

CAS — 139-07-1.

ATC — D09AA05.

ATC Vet — QD09AA05.

UNII — Y5A751G47H.

NOTE. The name Lauralkonium Chloride is also a *rINN* for another quaternary ammonium compound ($C_{29}H_{44}ClNO_2$; CAS – 19486-61-4).

Profile

Benzododecinium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in mouthwashes, eye preparations, and nasal sprays and solutions for the treatment of minor infections. It has also been used as a spermicide. Benzododecinium chloride has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Ajatin; *Fr.*: Rhinedrine.

Multi-ingredient Preparations. *Cz.*: Ophtal; *Fr.*: Prorhinel; Sedacollyre†; *Switz.*: Kemerhinose†; Prorhinel.

Benzoxonium Chloride *(rINN)*

Benzoxonii Chloridum; Benzoxonio, cloruro de; Benzoxonium, Chlorure de; Cloruro de benzoxonio; Бензоксония Хлорид.

Benzyldodecylbis(2-hydroxyethyl)ammonium chloride.

$C_{23}H_{42}ClNO_2$=400.0

CAS — 19379-90-9.

ATC — A01AB14; D08AJ05.

ATC Vet — QA01AB14; QD08AJ05.

UNII — 12IMO9R11X.

Profile

Benzoxonium chloride is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also used for instrument disinfection. Allergic contact dermatitis from benzoxonium chloride has been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Orofar; *Chile*: Bialcol; *Gr.*: Orocil; *Ital.*: Bactofen; Bialcol.

Multi-ingredient Preparations. *Belg.*: Orofar Lidocaine; *Braz.*: Halog Capilar; *Chile*: Alcolex†; *Cz.*: Orofar; *Gr.*: Orocil Lido; *Hung.*: Mebucain; Pedimed; *Israel*: Merfen; Vita-Merfen NF; *Philipp.*: Orofar-L; *Pol.*: Orofar; *Rus.*: Theraflu Lar (Терафлю Лар); *Switz.*: Mebuca-Orange; Mebucalers †; Mebucaliquid; Mebucaspray; Merfen; Orofar; Vita-Merfen; *Turk.*: Merfen; Vita-Merfen; *Ukr.*: Theraflu LAR (Терафлю ЛАР)†.

Benzyl Alcohol *(rINN)*

Alcohol benzílico; Alcohol Benzylicus; Alcoholum Benzylicum; Alcool Benzylique; Alkohol Benzylowy; Bensylalkohol; Bentsyylialkoholi; Benzenemethanol; Benzil-alkohol; Benzilo alkoholis; Benzylalkohol; Benzylique, alcool; Fenilmetanol; Phenylcarbinol; Phenylmethanol; Бензиловый Спирт.

$C_6H_5CH_2OH$=108.1

CAS — 100-51-6.

UNII — LKG8494WBH.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Benzyl Alcohol). A clear colourless, oily liquid. Soluble in water; miscible with alcohol, and with fatty and essential oils. Store under nitrogen in airtight containers at a temperature of 2 degrees to 8 degrees. Protect from light.

USNF 31: (Benzyl Alcohol). A clear, colourless, oily liquid. Sparingly soluble in water; freely soluble in alcohol (50%); miscible with alcohol, with chloroform, and with ether. It is neutral to litmus. Store in airtight containers. Protect from light.

Incompatibility. Benzyl alcohol is incompatible with oxidising agents and strong acids. The antimicrobial activity may be reduced by nonionic surfactants and benzyl alcohol may be lost from solutions stored in polyethylene containers.

Stability. Benzyl alcohol oxidises to produce benzaldehyde and benzoic acid and oxidation may take place slowly on exposure to air. Benzaldehyde may also be produced on autoclaving.

Uses

Benzyl alcohol is used as an antimicrobial preservative. It is bacteriostatic mainly against Gram-positive organisms and some fungi. It is used in a range of pharmaceutical preparations in concentrations up to 2%. Concentrations of 5% or more are employed when it is used as a solubiliser. Benzyl alcohol is used as a preservative in foods and cosmetics. It is also used as a disinfectant at a concentration of 10%.

In addition to its antiseptic properties, concentrations of benzyl alcohol of up to 10% possess weak local anaesthetic and antipruritic activity.

A preparation containing 5% benzyl alcohol is used for the topical treatment of head pediculosis (p. 2147.3) in adults and children 6 months of age and older. It is inactive against the ova and a second application is needed after 7 days.

Adverse Effects and Precautions

Benzyl alcohol may produce hypersensitivity reactions, including local irritation and skin reactions.

The pure alcohol is irritant and requires handling with care; ingestion or inhalation can cause nausea, vomiting, diarrhoea, headache, and vertigo. Overexposure results in respiratory failure and CNS depression. However, concentrations of benzyl alcohol normally used are not associated with such effects.

There have been some instances of neurotoxic effects in patients given intrathecal injections that contained benzyl alcohol.

A fatal toxic syndrome in premature infants was attributed to benzyl alcohol present as a preservative in solutions used to flush intravenous catheters. This has led to restriction on the use of benzyl alcohol in neonates and young children, (see p. 1740.1).

Effects on the lungs. Severe bronchitis and haemoptysis was reported in a patient with obstructive pulmonary disease who, over a period of 2 years, had inhaled salbutamol nebuliser solution diluted with a bacteriostatic sodium chloride solution containing benzyl alcohol.[1]

1. Reynolds RD. Nebulizer bronchitis induced by bacteriostatic saline. *JAMA* 1990; 264: 35.

Effects on the nervous system. Rapid development of flaccid areflexic paraplegia, total anaesthesia below the groin, and radicular abdominal pain occurred in a 64-year-old man after a lumbar intrathecal injection of cytarabine that contained 1.5% benzyl alcohol.[1] The patient recovered fully after 100 mL of CSF was replaced with sodium chloride 0.9% and 40 mg of methylprednisolone. Intrathecal

injections of cytarabine dissolved in sterile distilled water before and after the episode of paraplegia caused no neurologic symptoms. On reviewing 20 other cases of paraparesis associated with methotrexate or cytarabine intrathecal injections, benzyl alcohol had been used as a preservative in 7. Of these, 4 developed neurotoxicity immediately; in the other 3 it did not develop for between 6 and 48 hours. The duration varied. One patient did not improve, one made a partial recovery, a third took 6 weeks to recover, another took 5 days; yet 2 patients recovered within 1½ to 2½ hours while the final patient had only transient effects.

1. Hahn AF, *et al.* Paraparesis following intrathecal chemotherapy. *Neurology* 1983; 33: 1032–8.

Hypersensitivity. Hypersensitivity reactions to benzyl alcohol have been reported.[1-3]

1. Grant JA, *et al.* Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med* 1982; 306: 108.
2. Shmunes E. Allergic dermatitis to benzyl alcohol in an injectable solution. *Arch Dermatol* 1984; 120: 1200–1.
3. Wilson JP, *et al.* Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm* 1986; 20: 689–91.

Neonates. During 1981 and 1982 reports were published from 2 centres in the USA[1-3] of 20 deaths in low-birth-weight neonates attributed to the use of benzyl alcohol as a preservative in solutions used to flush their umbilical catheters and in some cases also to dilute their medication. The neonates suffered a toxic syndrome whose features included metabolic acidosis, symptoms of progressive encephalopathy, intracranial haemorrhage, and respiratory depression with gasping.

These deaths prompted the FDA[4] to recommend that benzyl alcohol should not be used in such flushing solutions; sodium chloride injection 0.9% without preservative should be used instead. The FDA had also advised against the use of benzyl alcohol or any preservative in fluids being used for the dilution or reconstitution of medicines for the newborn.

Those reporting the deaths[2,3] considered that the toxic syndrome could have been caused by the accumulation of the benzoic acid metabolite of benzyl alcohol, which could not be handled effectively by the immature liver; given the very low weight of the neonates they would have been receiving a comparatively high dose of benzyl alcohol. In commenting on the problem, the American Academy of Pediatrics[5] agreed that the FDA's warning was warranted, but pointed out that there was no evidence from controlled studies to confirm that benzyl alcohol was responsible.

1. Gershanik JJ, *et al.* The gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res* 1981; 29: 895A.
2. Brown WJ, *et al.* Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet* 1982; i: 1250.
3. Gershanik J, *et al.* The gasping syndrome and benzyl alcohol poisoning. *N Engl J Med* 1982; 307: 1384–8.
4. Anonymous. Benzyl alcohol may be toxic to newborns. *FDA Drug Bull* 1982; 12: 10–11.
5. American Academy of Pediatrics. Benzyl alcohol: toxic agent in neonatal use. *Pediatrics* 1983; 72: 356–7.

Pharmacokinetics

Benzyl alcohol is metabolised to benzoic acid. This is conjugated with glycine in the liver to form hippuric acid which is excreted in the urine. Benzaldehyde and benzoic acid are degradation products *in vitro*.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: NeutraLice Advance; *S. Afr.*: Cepacol; *USA*: Ulesfia; Zilactin-L; Zilactin.

Multi-ingredient Preparations. *Arg.*: Pastillas Pagliano; Standard XXI; *Austral.*: Coso†; Soothe'n Heal†; *Belg.*: Purigel Crisp†; Purigel NF; *Chile*: Aucusik; Lerfimin; *Denm.*: Doloproct; *Fr.*: Biseptine; Dermaspraid Antiseptique†; Pastilles Medicinales Vicks; Sarnol; *Ger.*: Autoderm Extra; Spitacid; *India*: Accept; Acent; Alto; Arflur; Binpain; Dacpar; Delaxin-M; Dicloran-MS; Dicnap; Dion; Diplofen; Diptase; Dolec Plus; Duoflam Spy; Felini; Genoplex Forte; Imidil B; Imidil Plus; Intragesic; Jusgo; Kloser-D; L-Divon; Lenex; Linif; Nacmol Plus; Nicfofen; Onspot; Opinac; Oronac; Orthodac; *Irl.*: Sudocrem; *Israel*: Otomycin; *Ital.*: Foille Scottature; Foille Sole; Neo Borocillina Ant Oro; Pitiren; Prurex; Skab 2†; *S.Afr.*: Medi-Keel A; *Spain*: Acerbiol†; *Switz.*: Skinsept; *UK*: Sudocrem; *Ukr.*: Sudocrem (Судокрем); *USA*: MouthKote O/R; MuGard; Oragesic; Super Ivy Dry; Topic; Tucks.

Biclotymol *(rINN)*

Biclotimol; Biclotymolum; Биклотимол.
2,2'-Methylenebis(6-chlorothymole).
$C_{21}H_{26}Cl_2O_2$=381.3
CAS — 15686-33-6.
UNII — W4K0AE8XW9.

Profile

Biclotymol is a phenolic antiseptic that is used in lozenges and sprays for mouth and throat infections. It is also an ingredient of cough preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Hexaspray; Humex Mal de Gorge; Sagaspray†; Solutricine Maux de Gorge; *Hong Kong*: Hexaspray; *Port.*: Hexaspray; *Rus.*: Hexaspray (Гексаспрей); *Ukr.*: Hexaspray (Гексаспрей).

Multi-ingredient Preparations. *Fr.*: Hexalyse; Hexapneumine†; Hexapneumine; Hexarhume; *Hong Kong*: Hexalyse; Hexapneumine†; Hexapneumine: *Rus.*: Hexalyse (Гексализ); *Ukr.*: Hexalyse (Гексализ); Hexapneumine for Children (Гексапневмин Для Детей)†.

Brilliant Green

CI Basic Green 1; Colour Index No. 42040; Diamond Green G; Emerald Green; Ethyl Green; Malachite Green G; Solid Green; Verde brillante; Viride Nitens; Бриллиантовый Зелёный.
4-(4-Diethylaminobenzhydrylidene)cyclohexa-2,5-dien-1-ylidenediethylammonium hydrogen sulphate.
$C_{27}H_{34}N_2O_4S$=482.6
CAS — 633-03-4.
UNII — G0LS43D370.

NOTE. The name Emerald Green has also been used for copper acetoarsenite.

Profile

Brilliant green is a triphenylmethane antiseptic dye with actions similar to those of methylrosanilinium chloride (p. 1761.1). Its activity is greatly reduced in the presence of serum.

A gel containing brilliant green 0.5% with lactic acid was formerly used in the treatment of skin ulcers.

An alcoholic solution of brilliant green 0.5% and methylrosanilinium chloride 0.5% (Bonney's Blue) was formerly used for disinfecting the skin, but concern over evidence of *animal* carcinogenicity with methylrosanilinium chloride has led to a decline in its use. A solution of the two disinfectants has been used for marking incisions before surgery.

There have been occasional reports of sensitivity to brilliant green.

Adverse effects. For a report of necrotic skin reactions after application of a 1% solution of brilliant green to stripped skin, see under the Adverse Effects of Methylrosanilinium Chloride, p. 1761.2.

Bromchlorophen

Bromchlorophene; Bromochlorophane; Bromoclorofeno.
2,2'-Methylenebis[6-bromo-4-chlorophenol].
$C_{13}H_8Br_2Cl_2O_2$=426.9
CAS — 15435-29-7.
UNII — 2JZV1D2GW7.

Profile

Bromchlorophen is a halogenated bisphenol antiseptic more active against Gram-positive than Gram-negative bacteria. It is used for disinfection of the hands and skin. It has also been used in deodorants and toothpastes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Dibromol†.

Bromsalans

Bromosalicilanilidas.
CAS — 55830-61-0.

Description. Bromsalans are a series of brominated salicylanilides that possess antimicrobial activity.

Dibromsalan *(USAN, pINN)*

Dibromsalán; Dibromsalanum; NSC-20527; Дибромсалан.
4',5-Dibromosalicylanilide; 5-Bromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
$C_{13}H_9Br_2NO_2$=371.0
CAS — 87-12-7.
UNII — N9900K2RBT.

Metabromsalan *(USAN, pINN)*

Metabromsalán; Metabromsalan; Metabromsalanum; NSC-526280; Метабромсалан.
3,5-Dibromosalicylanilide; 3,5-Dibromo-2-hydroxy-*N*-phenylbenzamide.
$C_{13}H_9Br_2NO_2$=371.0
CAS — 2577-72-2.
UNII — 8Q21Y09R21.

Tribromsalan *(BAN, USAN, rINN)*

ET-394; NSC-20526; TBS; Tribromsalán; Tribromsalanum; Трибромсалан.
3,4',5-Tribromosalicylanilide; 3,5-Dibromo-*N*-(4-bromophenyl)-2-hydroxybenzamide.
$C_{13}H_8Br_3NO_2$=449.9
CAS — 87-10-5.
UNII — 6MCE3VTF0O.

Profile

Bromsalans have antibacterial and antifungal activity and have been used in medicated soaps, but there have been many reports of photosensitivity arising from this use.

Bronopol *(BAN, rINN)*

Bronopolum; Бронопол.
2-Bromo-2-nitropropane-1,3-diol.
$C_3H_6BrNO_4$=200.0
CAS — 52-51-7.
ATC Vet — QD01AE91.
UNII — 6PU1E16C9W.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2014: (Bronopol). White or almost white crystals or crystalline powder, odourless or almost odourless. Freely soluble in water and in alcohol; slightly soluble in glycerol and in liquid paraffin. A 1% solution in water has a pH of 5.0 to 7.0. Protect from light.

Incompatibility. The activity of bronopol can be reduced by sodium metabisulfite, sodium thiosulfate, cysteine hydrochloride, and compounds with a thiol group. Incompatibility with unprotected aluminium affects packaging.

Stability. The stability of bronopol is affected by increases in temperature and by increases in pH above 8.

Creams and shampoos containing bronopol 0.01% as a preservative were found to contain free nitrite and, as a result of amines present in the preparations, nitrosamines.[1] It was recommended that nitrosamine formation could be reduced in preparations containing amines and bronopol by limiting the bronopol concentration to 0.01% and inclusion of alpha tocopherol 0.2% or butylated hydroxytoluene 0.05%.

1. Dunnett PC, Telling GM. Study of the fate of bronopol and the effects of antioxidants on *N*-nitrosamine formation in shampoos and skin creams. *Int J Cosmet Sci* 1984; 6: 241–7.

Uses

Bronopol is active against a wide range of bacteria, including *Pseudomonas aeruginosa*, but is less active against moulds and yeasts. Bronopol is used as a preservative in shampoos, cosmetics, and both topical and oral pharmaceutical preparations; concentrations in pharmaceutical preparations range from 0.01 to 0.1%, with the usual concentration being 0.02%. It is also used for its antimicrobial properties in various industrial applications, including in air conditioning systems.

Adverse Effects

Bronopol may be irritant when applied topically and cases of contact dermatitis have been reported.

Pharmacokinetics

Bronopol is absorbed following topical use.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Antiseptic Hand Soap.

Butylated Hydroxyanisole *(BAN)*

BHA; Butilhidroksianizolas; Butilhidroxianisol; Butil-hidroxianizol; Butilidrossianisolo; Butylhydroxianisol; Butylhydroxyanisol; Butylhydroxyanisole; Butylhydroxyanisolum; Butylohydroksyanizol; Butyylihydroksianisoli; E320; Бутилгидроксианизол.

2-*tert*-Butyl-4-methoxyphenol; 2-(1,1-dimethylethyl)-4-methoxyphenol.
$C_{11}H_{16}O_2$=180.2
CAS — 25013-16-5.
UNII — REK4960K2U.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Butylhydroxyanisole; Butylated Hydroxyanisole BP 2014). A white, yellowish, or slightly pinkish, crystalline powder. It contains not more than 10% of 3-(1,1-dimethylethyl)-4-methoxyphenol. Practically insoluble in water; freely soluble in alcohol and in fatty oils; very soluble in dichloromethane; it dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Butylated Hydroxyanisole). A white, or slightly yellow, waxy solid with a faint characteristic odour. Insoluble in water; soluble 1 in 4 of alcohol, 1 in 2 of chloroform, and 1 in 1.2 of ether; freely soluble in propylene glycol.

Incompatibility. Butylated hydroxyanisole is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Uses

Butylated hydroxyanisole is an antoxidant with some antimicrobial activity. It is used as a preservative in cosmetics and foods as well as pharmaceutical preparations, particularly to delay or prevent oxidative rancidity of fats and oils in concentrations of up to 0.02%; higher concentrations have been used for essential oils. It is also used to prevent the loss of activity of oil-soluble vitamins. To improve efficacy, butylated hydroxyanisole is frequently used with other antoxidants such as butylated hydroxytoluene or an alkyl gallate and with sequestrants or synergists such as citric acid.

Commercial supplies of butylated hydroxyanisole used in food technology consist of mixtures of the 2-*tert* and 3-*tert* isomers.

Use in food. In the UK the Food Advisory Committee has recommended that the use of butylated hydroxyanisole and butylated hydroxytoluene should no longer be permitted as additives for infant formulas as they are no longer required for the economic manufacture of vitamin A and vitamin A esters.[1]

1. MAFF. Food Advisory Committee: report on the review of the use of additives in foods specially prepared for infants and young children. *FdAC/REP/12.* London: HMSO,1992.

Adverse Effects

Butylated hydroxyanisole can be irritant to the eyes, skin, and mucous membranes and can cause depigmentation. There are also reports of contact urticaria.

Carcinogenicity. There has been concern as to whether butylated hydroxyanisole may be a carcinogen.[1,2] These concerns stem from a study in which *rodents* given food containing 1 to 2% butylated hydroxyanisole developed squamous cell carcinoma of the forestomach. No similar malignancies were found in studies with *animals* that do not have a forestomach. The IARC has concluded[2] that there is sufficient evidence for the carcinogenicity of butylated hydroxyanisole in *animals* but that there is no data on its carcinogenicity in humans.

1. FAO/WHO. Evaluation of certain food additives and contaminants: thirty-third report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 776* 1989. Available at: http://libdoc.who.int/trs/WHO_TRS_776.pdf (accessed 27/08/08)
2. IARC/WHO. Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 40* 1986. Available at: http://monographs.iarc.fr/ENG/Monographs/vol40/volume40.pdf (accessed 23/05/06)

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed, see under Adverse Effects in Alkyl Gallates (p. 1736.2).

Pharmacokinetics

Butylated hydroxyanisole is absorbed from the gastrointestinal tract, then metabolised and conjugated, and excreted in the urine; less than 1% is excreted in the urine as unchanged drug within 24 hours of ingestion.

Butylated Hydroxytoluene *(BAN)*

BHT; Butilhidroksitoluenas; Butilhidroxitolueno; Butil-hidroxitoluol; Butylhydroxitoluen; Butylhydroxitoluenum; Butylhydroxytoluen; Butylhydroxytoluene; Butylhydroxytoluène; Butylhydroxytoluenum; Butylhydroxytoluol; Butylohydroksytoluen; Butylylhydroksitolueeni; E321; Бутилгидрокситолуол; Бутилированный Гидрокситолуол.
2,6-Di-*tert*-butyl-*p*-cresol.
$C_{15}H_{24}O$=220.4
CAS — 128-37-0.
UNII — 1P9D0Z171K.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Butylhydroxytoluene; Butylated Hydroxytoluene BP 2014). A white or yellowish-white, crystalline powder. F.p. 69 degrees to 70 degrees. Practically insoluble in water; freely soluble in alcohol and in vegetable oils; very soluble in acetone.

USNF 31: (Butylated Hydroxytoluene). A white crystalline solid with a faint characteristic odour. Insoluble in water and in propylene glycol; soluble 1 in 4 of alcohol and 1 in 1.1 of chloroform and of ether.

Incompatibility. Butylated hydroxytoluene is incompatible with oxidising agents and ferric salts. Traces of metals can cause loss of activity.

Uses

Butylated hydroxytoluene is an antoxidant with uses similar to those of Butylated Hydroxyanisole, above.

Adverse Effects

As for Butylated Hydroxyanisole, above.

Effects on the blood. For a report of methaemoglobinaemia associated with the antoxidants (butylated hydroxyanisole, butylated hydroxytoluene, and propyl gallate) used to preserve the oil in a soybean infant feed formula, see under Adverse Effects in Alkyl Gallates, p. 1736.2.

Poisoning. A 22-year-old woman had severe epigastric cramping, nausea and vomiting, and generalised weakness, followed by dizziness, confusion, and a brief loss of consciousness after ingesting 4 g of butylated hydroxytoluene. She recovered after conservative treatment, which was given 2 days later. The antoxidant had been taken as an unauthorised remedy for genital herpes simplex.[1]

1. Shilan DM, Goldstone J. Toxicity of butylated hydroxytoluene. *N Engl J Med* 1986; 314: 648–9.

Pharmacokinetics

Butylated hydroxytoluene is readily absorbed from the gastrointestinal tract. It is excreted in the urine mainly as glucuronide conjugates of oxidation products.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Proseptine-Plus†.

Cadexomer-Iodine *(BAN)*

Cadexomer Iodine (USAN); Cadexomer Iodine; Cadexomer-jod; Cadexómero yodado; Cadexomerum Iodum; Kadeksomeerijodi; Кадексомера-йодин.
2-Hydroxymethylene cross-linked (1→4)-α-D-glucan carboxymethyl ether containing iodine.
CAS — 94820-09-4.
ATC — D03AX01.
ATC Vet — QD03AX01.

Uses and Administration

Cadexomer-iodine, like povidone-iodine (p. 1767.1), is an iodophore that releases iodine. It is used for its absorbent and antiseptic properties in the management of venous leg ulcers and pressure sores. It is applied as a powder, ointment, or paste containing iodine 0.9%; sufficient powder or ointment should be applied to form a layer about 3 mm thick. Treatment should not usually be continued for more than 3 months.

Adverse Effects and Precautions

As for Povidone-Iodine, p. 1767.2. Some patients have stinging and erythema on application of cadexomer-iodine to their ulcers. Free iodine is released during exposure of cadexomer-iodine preparations to wound exudate and absorption of iodine may occur. Prolonged treatment with cadexomer-iodine should be given with caution in patients with thyroid disorders.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies cadexomer-iodine as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Iodosorb; *Canad.*: Iodosorb; *Ger.*: Iodosorb; *Gr.*: Iodosorb; *Irl.*: Iodoflex; *Ital.*: Iodosorb; *Malaysia*: Iodosorb; *Neth.*: Iodosorb†; *S.Afr.*: Iodosorb†; *UK*: Iodoflex; Iodosorb; *USA*: Iodosorb.

Calcium Peroxide

Calcium Dioxide; E930; Пероксид Кальция.
CaO_2=72.08
CAS — 1305-79-9.
UNII — 7FRO2ENO91.

Profile

The action of calcium peroxide is similar to that of hydrogen peroxide (p. 1755.2). Calcium peroxide is used in dental products for tooth whitening. It is also used as a flour bleaching and improving agent.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Hexiben.

Carbaethopendecinium Bromide

Carbethopendecinii Bromidum; Carbethoxypentadecyltrimethylammonium Bromide; Karbethopendecinium bromid.
1-Ethoxy-*N*,*N*,*N*-trimethyl-1-oxo-2-hexadecanaminium bromide.
$C_{21}H_{44}NO_2Br$=422.5
CAS — 10567-02-9.

Profile

Carbaethopendecinium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in topical preparations for disinfection of skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Cz.*: Mukoseptonex; Ophthalmo-Septonex; Septonex.

Multi-ingredient Preparations. *Cz.*: Mesocain; Mukoseptonex E; Ophthalmo-Septonex; Septonex Plus; Septonex; Triamcinolon.

Cetalkonium Chloride *(BAN, USAN, rINN)*

Cetalconio, cloruro de; Cetalkonii Chloridum; Cétalkonium, Chlorure de; Cloruro de cetalconio; NSC-32942; Цеталкония Хлорид.
Benzylhexadecyldimethylammonium chloride.
$C_{25}H_{46}ClN$=396.1
CAS — 122-18-9.
UNII — 8547401N9D.

Profile

Cetalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in a variety of topical preparations in the treatment of minor infections of the mouth and throat. It has also been used in the treatment of eye infections. Cetalkonium bromide has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Pansoral; *Austral.*: Bonjela; Sedagel; *Belg.*: Teejel; *Braz.*: Pondicilina; *Canad.*: Bionet; *Fr.*: Pansoral; *Gr.*: Mundisal; *Hong Kong*: Bonjela; *Hung.*: Mundisal; *Irl.*: Bonjela; Teejel†; *Israel*: Baby Gum; Bonjela†; Teejel; *Malaysia*: Bonjela; Cationorm; *NZ*: Bonjela; *Pol.*: Sachol zel Stomatologiczny; *Rus.*: Cholisal (Холисал); Pansoral (Пансорал); *S.Afr.*: Bonjela; *Singapore*: Bonjela; *Switz.*: Pansoral†; Tenderdol; *Thai.*: Bonjela; *UK*: Bonjela Cool Mint; Bonjela Teething Gel; Bonjela; *Ukr.*: Cholisal (Холисал); *USA*: Babee.

Cethexonium Bromide (rINNM)

Bromuro de cetexonio; Cetexonio, bromuro de; Cethexonil Bromidum; Céthexonium, Bromure de; Цетексония бромид.
Hexadecyl(2-hydroxycyclohexyl)dimethylammonium bromide.
$C_{24}H_{50}BrNO$=448.6
CAS — 6810-42-0 (cethexonium); 1794-74-7 (cethexonium bromide).
UNII — F3T95WRD7W.

Profile

Cethexonium bromide is a quaternary ammonium antiseptic with properties similar to those of other cationic surfactants (see Cetrimide, below). It is used in preparations for the local treatment of minor infections of the eye, nose, and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Biocidan; Monosept; Sedacollyre.

Multi-ingredient Preparations. *Fr.*: Biocidan.

Cetrimide (BAN, rINN)

Cetrimid; Cetrimida; Cetrimidas; Cétrimide; Cetrimidum; Cetrymid; Setrimid; Setrimidi; Цетримид.
CAS — 1119-97-7 (trimethyltetradecylammonium bromide); 1119-94-4 (dodecyltrimethylammonium bromide); 8044-71-1 (cetrimide).
ATC — D08AJ04; D11AC01.
ATC Vet — QD08AJ04; QD11AC01.
UNII — 24OSH2NL8N.

NOTE. The name cetrimonium bromide was often formerly used for cetrimide. Cetrimonium bromide (see below) is hexadecyltrimethylammonium bromide.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.*

Br. also includes strong cetrimide solution.

Ph. Eur. 8: (Cetrimide). It consists of trimethyltetradecylammonium bromide (=tetradonium bromide (*rINN*)) and may contain smaller amounts of dodecyltrimethylammonium bromide and hexadecyltrimethylammonium bromide (=cetrimonium bromide, below). A white or almost white, voluminous, free-flowing powder. Freely soluble in water and in alcohol. A 2.0% solution in water froths copiously when shaken.

BP 2014: (Strong Cetrimide Solution). It is an aqueous solution of cetrimide. It contains 20 to 40% w/v of cetrimide, calculated as $C_{17}H_{34}BrN$ and up to 10% alcohol or isopropyl alcohol, or both; alcohol may be replaced by industrial methylated spirit. It may be perfumed and may contain colouring matter. Store at a temperature above 15 degrees.

Incompatibility. Cetrimide is incompatible with soaps and other anionic surfactants, bentonite, iodine, phenylmercuric nitrate, and alkali hydroxides. Aqueous solutions react with metals.

Uses and Administration

Cetrimide is a quaternary ammonium antiseptic with actions and uses typical of cationic surfactants. These surfactants dissociate in aqueous solution into a relatively large and complex cation that is responsible for the surface activity and a smaller inactive anion. In addition to emulsifying and detergent properties, quaternary ammonium compounds have bactericidal activity against Gram-positive and, at a higher concentration, against some Gram-negative bacteria. Some *Pseudomonas* spp. are particularly resistant as are strains of *Mycobacterium tuberculosis*. They are ineffective against bacterial spores, have variable antifungal activity, and are effective against some viruses.

Quaternary ammonium compounds are most effective in neutral or slightly alkaline solution and their bactericidal activity is appreciably reduced in acid media; their activity is enhanced by alcohols.

Like other quaternary ammonium compounds, notably benzalkonium chloride (p. 1737.1), cetrimide has been employed for cleansing skin, wounds (but see under Wound Disinfection, p. 1732.2), and burns. For these purposes it has been used as a 0.1 to 1.0% aqueous solution, generally prepared by dilution of a more concentrated solution, or as a cream or spray containing 0.5%. However, a mixture of cetrimide with chlorhexidine (p. 1743.2) has often been preferred to cetrimide alone. This combination is also used in a lotion for acne (p. 1682.2).

Solutions containing up to 10% of cetrimide have been used as shampoos to remove the scales in seborrhoeic dermatitis (p. 1689.1).

Cetrimide solution 0.5 or 1% has been used as a scolicide to irrigate hydatid cysts during surgery (see Echinococcosis, p. 145.2) but systemic adverse effects have been reported (see below).

Cetrimide and benzalkonium chloride are also used as preservatives in cosmetics and pharmaceutical formulations including eye drops and in disinfecting solutions for hard contact lenses; neither compound should be used for disinfection of soft contact lenses.

Cetrimide is also present in some emulsifying preparations such as Cetrimide Emulsifying Ointment (BP 2014).

Adverse Effects and Treatment

At the concentrations used on the skin, solutions of cetrimide and other quaternary compounds do not generally cause irritation, but some patients become hypersensitive to cetrimide after repeated applications. Cetrimide powder is reported to be irritant. There have been rare reports of burns with concentrated solutions of cetrimide.

If ingested, cetrimide and other quaternary ammonium compounds cause nausea and vomiting; strong solutions may cause oesophageal damage and necrosis. They have depolarising muscle relaxant properties and toxic symptoms include dyspnoea and cyanosis due to paralysis of the respiratory muscles, possibly leading to asphyxia. CNS depression (sometimes preceded by excitement and convulsions), hypotension, coma, and death may also occur. Accidental intra-uterine or intravenous administration may cause haemolysis and pulmonary embolism.

Treatment of poisoning is symptomatic; demulcents and diluents may be given if necessary but emesis and lavage should be avoided, particularly if concentrated solutions have been ingested. Activated charcoal may be considered if the patient presents within an hour of ingestion. CNS stimulants and cholinesterase inhibitors are reported not to reverse paralysis due to cetrimide intoxication although sympathomimetics have been tried. Corticosteroids may reduce oropharyngeal oedema.

Effects after cyst irrigation. Adverse effects after irrigation with cetrimide solutions in the treatment of hydatid cysts have included chemical peritonitis,[1] methaemoglobinaemia with cyanosis,[2] and metabolic acidosis.[3]

1. Gilchrist DS. Chemical peritonitis after cetrimide washout in hydatid-cyst surgery. *Lancet* 1979; **ii**: 1374.
2. Baraka A, *et al.* Cetrimide-induced methaemoglobinaemia after surgical excision of hydatid cyst. *Lancet* 1980; **ii**: 88–9.
3. Mombiano P, *et al.* Metabolic acidosis induced by cetrimonium bromide. *Lancet* 1984; **ii**: 1045.

Poisoning. The fatal dose of quaternary ammonium compounds was estimated to be 1 to 3 g.[1]

1. Arena JM. Poisonings and other health hazards associated with use of detergents. *JAMA* 1964; **190**: 56–8.

Precautions

Prolonged and repeated applications of cetrimide to the skin are inadvisable as hypersensitivity may occur. Contact with the eyes, brain, meninges, and middle ear should be avoided. Cetrimide is for external use only and should not be used in body cavities or as an enema.

Quaternary ammonium compounds are not reliable for sterilising surgical instruments and beat-labile articles. The antimicrobial activity of quaternary ammonium compounds may be reduced through absorption, or through combination with organic matter, or by reducing pH.

Solutions of quaternary ammonium compounds should not be used for disinfection of soft contact lenses.

Aqueous solutions of cetrimide or other quaternary ammonium disinfectants may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Handling. Cetrimide powder is irritant; it has been recommended that the nose and mouth should be protected by a mask when working with the powder[1] and eyes should be protected by goggles.

1. Jacobs JY. Work hazards from drug handling. *Pharm J* 1984; **233**: 195–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Boucren; Sorbicet; *Austral.*: Skin-Prep with Cetramide; *Belg.*: Aseptiderm; *Fr.*: Cetavlon; Sterilene; *Gr.*: Cetavlon; *Hong Kong*: Cetrol†; *India*: Aceptik; Cetavlon; Cetrilak; Cetrim; Gemide; *Irl.*: Vesagex; *Malaysia*: Dermoplex Antiseptic; *Port.*: Cetavlex; *Turk.*: Cetyl; *UK*: Cetavlex; Medi-Prep; Medicaid; Richmond Antiseptic Cream; Vesagex.

Multi-ingredient Preparations. *Arg.*: Cerosporin; Jabonacid; Otidrops; Otocalmia Biotic; Sincerum; *Austral.*: Acnederm Foaming Wash†; Dimethicream; Hamilton Pine Tar with Menthol; Medi Creme; Microshield Antiseptic†; Savlon Antiseptic; Soov Bite; Soov Burn; Soov Cream; *Austria*: Lemocin; Xylonor; *Belg.*: Lemocin; *Canad.*: Savlodil†; Xylonor; *Fin.*: Lakrimont; *Fr.*: Biodicaïne†; Dicagel†; Lysocalmspray†; Rectoquotane; Xogel; Xylonor; Ziacaine; Ziagel; *Gr.*: Hibicet; *Hong Kong*: Acnederm Wash; Borraginol-N†; DPH with Calamine†; Hamilton Skin Repair†; Medicreme†; Phytocine†; Soov Bite; Soov Cream; Tri-Gel†; Zinsomine; *India*: Aceptik-HC; Aceptik-LA; Agloscab; Antiscab; Clenora; Clenorush; Coral; Dentakind; Dermogard; Endruff; Escab Plus; Freescab; Gamaley; Gamazex; GBTop; Gynocream; Intalon; Iteol-3; Klinit; Microgard; Microshield Antiseptic; New Iteol-3; Novascab; NT-Scab; O2-Fresh-GP; Ora-G; Scabine; Scarab; Siloderm; *Indon.*: Benzomid; Bioacne; Borraginol-N; Borraginol-S; Neo Resiguard; Pravlon†; *Irl.*: Cymex; Drapolene; Hibicet; Lypsyl Cold Sore Gel†; RBC†; Savlon; Sterets Tisept; Torbetol†; Xylonor; *Israel*: Cetrín; Savlor; Tisept; Travasept; Xylonor; *Ital.*: Baxidin; Cetrexidin; Cetrifarm; Cetrisan†; Cuprosodio; Farvicett; Hibizene; Lidocaina Spray; Panseptil†; *Malaysia*: Acnederm Foaming Wash; Burnol Plus; Drapolene; Norash; Soov Bite; *Neth.*: Hibicet concentraat; Hibicet verdunning; *NZ*: Acnederm Foaming Wash†; Medicreme†; Savlon; Soov Bite; Soov Burn; Soov Cream; Soov Gel; *Philipp.*: Drapolene; *Rus.*: Drapolene (Драполен); *S.Afr.*: Germolene†; Orocaine; Savlon; Siopel; Trochain; *Singapore*: Acnederm Foaming Wash; Burnol Plus; Drapolene; Napitol; Norash; Soov Bite; Soov Cream; Tisept; *Switz.*: Xylonor; *Thai.*: Bacard†; Bactricide; Burnol Plus; Chlorhex-C†; Clocimide; Dekka; Dekkalon; Drapolene; Prebac; Hibicet†; Inhibac; Killa; Napilene; Septol-C; Septrex; *Turk.*: Deriseptol; Drapolene†; Savlex; Savlosol; Savonol; Savrolin; Setilin; *UK*: Ceanel; Cetanorm; Cymex; Dermidex; Drapolene; Lypsyl Cold Sore Gel; Neo Baby Cream; Quinoderm Antibacterial Face Wash; Savlon Antiseptic Cream; Savlon Antiseptic Liquid; Siopel; Tisept; Torbetol; Travasept†; *Ukr.*: Drapolen (Драполен); *USA*: Scadan.

Pharmacopoeial Preparations
BP 2014: Cetrimide Cream; Cetrimide Emulsifying Ointment; Cetrimide Solution.

Cetrimonium Bromide (BAN, rINN)

Bromuro de cetrimonio; Cetrimonii Bromidum; Cetrimonio, bromuro de; Cétrimonium, Bromure de; Cetylotrimetyloamoniowy bromek; Cetyltrimethylammonium Bromide; CTAB; Цетримония бромид.
Hexadecyltrimethylammonium bromide.
$C_{19}H_{42}BrN$=364.5
CAS — 6899-10-1 (cetrimonium); 57-09-0 (cetrimonium bromide).
ATC — D08AJ02; R02AA17.
ATC Vet — QD08AJ02; QR02AA17.
UNII — L64N7M98WR.

NOTE. The name cetrimonium bromide was formerly applied to cetrimide (see above).

Pharmacopoeias. In *USNF.*

USNF 31: (Cetrimonium Bromide). A white to creamy white, voluminous, free-flowing powder, with a characteristic faint odour. Freely soluble in water and in alcohol; practically insoluble in ether.

Cetrimonium Chloride (BAN, rINNM)

Cetrimonii Chloridum; Cetrimonio, cloruro de; Cétrimonium, Chlorure de; Cloruro de cetrimonio; Цетримония Хлорид.
Hexadecyltrimethylammonium chloride.
$C_{19}H_{42}ClN$=320.0
CAS — 112-02-7.
ATC — D08AJ02; R02AA17.
ATC Vet — QD08AJ02; QR02AA17.
UNII — UC9PE95IBP.

Profile

Cetrimonium bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, above). Cetrimonium chloride and cetrimonium tosilate are also used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Neo-Intol; Senol; Sterilene; *Switz.*: Aknex Cleaning†; Turisan†.

Multi-ingredient Preparations. *Arg.*: Bagoderm; Eryteal; Klorane Bebe Eryteal; *Belg.*: Cetavlex; HAC; Hacdil-S; *Braz.*: Amigdalol; Cetrilan; Drapolene; *Canad.*: Largal Ultra; Salvesept†; Xylonor; *China*: Drapolene (保芙); *Fr.*: Nostril†; *Ger.*: Lemocin†; *Gr.*: Buccasept†; *Indon.*: Lemocin; *Israel*: Clearocin; Lemocin; *Ital.*: Golamixin; Xylonor; *Mex.*: Dermatolona; *Pol.*: Cetriscabin†;

Spain: Diformiltricina†; Hongosan†; Xylonor; *Switz.*: Lemocin; Mebu; Septivon; Turexan Capilla†; *Venez.*: Kertyol.

Cetylpyridinium Chloride *(BAN, rINN)*

Cetilpiridinio cloridas; Cetilpiridinio, cloruro de; Cetilpiridinium-klorid; Cetylpyridinii Chloridum; Cetylpyridinii Chloridum Monohydricum; Cétylpyridinium, Chlorure de; Cetylpyridiniumchlorid; Cetylpyridinium-chlorid monohydrát; Cetylpyridiniumklorid; Cloruro de cetilpiridinio; Setilpiridinyum Klorür; Setyylipyridiniumkloridi; Цетилпиридиния Хлорид.

1-Hexadecylpyridinium chloride monohydrate.

$C_{21}H_{38}ClN,H_2O$=358.0

CAS — 7773-52-6 (cetylpyridinium); 123-03-5 (anhydrous cetylpyridinium chloride); 6004-24-6 (cetylpyridinium chloride, monohydrate).

ATC — B05CA01; D08AJ03; D09AA07; R02AA06.

ATC Vet — QB05CA01; QD08AJ03; QD09AA07; QR02AA06.

UNII — D9OM4SK49P (cetylpyridinium chloride) 6BR7T22E2S (anhydrous cetylpyridinium chloride).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Cetylpyridinium Chloride). A white or almost white powder, slightly soapy to the touch. Soluble in water, frothing copiously when shaken; soluble in alcohol.

USP 36: (Cetylpyridinium Chloride). A white powder with a slight characteristic odour. Soluble 1 in 4.5 of water and of chloroform, and 1 in 2.5 of alcohol; slightly soluble in ether and in benzene.

Incompatibility. Cetylpyridinium chloride is incompatible with soaps and other anionic surfactants.

Profile

Cetylpyridinium chloride is a quaternary pyridinium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used chiefly as lozenges or solutions for the treatment of minor infections of the mouth and throat. It is also used topically for the treatment of skin and eye infections.

Cetylpyridinium bromide is used similarly for minor mouth and throat disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Higiemax; *Austral.*: Cepacol; Dentyl; Lemsip Lozenges†; *Austria*: Dobendan; Halset; *Braz.*: Cepacol; Gargocetil; Gargomax; Laringex; *Canad.*: Antiseptic Oral Rinse; Cepacol†; Crest Pro-Health; Rince Bouche Antiseptique; Throat Lozenges; *Chile*: Freesept; *China*: Ai Nuo Tian Jian (爱诺天健); Ben Li (本力); Kaikeli (开科立); Liangqi (亮奇); Ya Liang (雅量); Yi Xin (依信); *Cz.*: Halset; Neoseptolete; *Fr.*: Novoptine; Sedacollyre; *Ger.*: Dobendan; Halstabletten akute†; *Hong Kong*: Cepacol; Cetocomp; *Hung.*: Halset; *India*: Kolq; *Irl.*: Merocets; *Ital.*: Bat; Batzeta; Borocaina Gola; Cetilsan; Citromed Soap; Exil; Farin Gola; Golacetin; Golafair; Neo Cepacol Pastiglie; Neo Formitrol; Periogard Plus; Physioattivo; Ragaden; Stomygen; *Mex.*: Trociletas; *Norw.*: Pyrisept; *NZ*: Cepacol; Lemsip Throat Lozenges; *Pol.*: Halset; Menthosept; Septolete Apple; Septolete Cherry; Septolete Lemon; *Port.*: Septus; *Rus.*: Septolete Neo (Септолете Нео); *S.Afr.*: Cepacol; Goldex Throat Lollies; Universal Throat Lollies†; *Singapore*: Cepacol; *Switz.*: Halset; *Thai.*: Cepacol; Hops†; Orasept; *Turk.*: Aseptol†; Penipastil; *UK*: Listermint; Merocets; *Ukr.*: Septolete with lemon/cherry/apple (Септолете); *USA*: Cepacol Mouthwash; Cepacol Throat; Choice DM Gentle Care; Scope; *Venez.*: Cepacol.

Multi-ingredient Preparations. *Arg.*: Ernex Duo; Periodil; Solumerin; *Austral.*: Cepacaine; Cepacol Cough; Cepacol Plus; Difflam Anti-inflammatory Lozenges with Cough Suppressant; Difflam Lozenges; Difflam Mouth Gel; Duro-Tuss Dry Cough; Gentlees; Sedagel; *Austria*: Coldistan; Dentinox†; Gurfix†; *Braz.*: Cepacaina; Cepacol Menta; Lima C; Malvona; Neopiridin; Noplak Max; Pondicilina; Psiu; Sanilin; Silencium; Silencium; *Canad.*: Cepacol Extra Strength†; Cepacol with Fluoride†; Green Antiseptic Mouthwash & Gargle†; Kank-A; Oral-B Anti-Bacterial with Fluoride; Throat Lozenges; *Chile*: Adolex; Aftagel Bucal; Halita; Kank-Eze; Oralfresh; Pancrit; Perio-Aid c Cloruro de Cetilpiridinio; Vitis Encias Colutorio; Vitis Encias Pasta; Vitis Orthodontic Colutorio; *Cz.*: Calgel; Neoseptolete Duo; Panlid†; *Fin.*: Bafucin; *Fr.*: Alodont; Codotussyl Maux de Gorge; Gum HaliControl; Gum HaliControl; Lysopaine; Parogencyl prevention gencives†; *Ger.*: Dobendan Dolo; Frubienzym†; Tyrosur; Wick Sulagil; *Gr.*: Bisoral; Rikospray Silicone; *Hong Kong*: Dentinox Teething Gel; Dettol†; Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Mouth Gel; Pharynx; *Hung.*: Mebucain; Tyrosur; *India*: Garlin; Kofarest; *Indon.*: Sentril†; *Irl.*: Anbesol; Merocaine; Merocets Plus; Rinstead; Vicks Original Cough Syrup Chesty; *Israel*: Cepadont†; Kank-A; *Ital.*: Delta 80 Plus; Delta 80; Ginvapast; Gola Action; Neo-Stomygen; Neo-Stomygen; Oral-B Collutorio Denti Gengive; Ridiodent; Rikospray; Stomygen; Tantum Orosan; *Jpn*: Colgen Gargle†; *Malaysia*: Cetylpyridinium B; Dentinox Teething Gel; Difflam Anti-inflammatory Lozenges (with Antibacterial); Difflam Anti-Inflammatory Lozenges (with cough suppressant); Difflam Mouth Gel; Orregel; Pharynx; *Mex.*: Cepacaina; Mentalgina; Trociletas B; *Neth.*: Agre-Gola†; *Norw.*: Asellit†; *NZ*: Cepacaine; Cepacol Anaesthetic†; Cepacol Cough Discs; Cepacol Sore Throat; Difflam Anti-inflammatory Antibacterial Lozenges; Difflam Cough; Difflam Mouth Gel; Duro-Tuss Lozenges; *Philipp.*: Difflam Orange; Kene; Xylorinse; *Pol.*: Calgel; Lidodent; Orofar Max; Septolete Plus; Tetesept†; Undofen; *Port.*: Dropcina; Mebocaina; *Rus.*: Calgel (Калгель); Grammidin Neo (Граммидин Нео); Grammidin with Anesthetic Neo (Граммидин с АнестетикОм Нео); Novosept (Новосепт Форте); Septolete Plus (Септолете Плюс); *S.Afr.*: Anbesol†; Andolex-C; Cepacaine; Cepacol Cough Discs; Cepacol Cough; Cetoxol†; Colphen†; Endcol Lozenges; Medi-Kain; Medi-Keel A; Medi-Keel A; Prodol†; Vagarsol; Vicks Acta Plus†; Vicks Cough Syrup†; *Singapore*: Dentinox Teething Gel; Difflam Anti-inflammatory Anti-Bacterial Lozenges; Difflam Cough Lozenges; Difflam Mouth Gel; Duro-Tuss Cough Lozenges; Pharynx; Soragel; *Spain*: Alcohocel†; Babysiton†; Farmalcohol†; *Swed.*: Bafucin; *Switz.*: Angiben; Angina MCC; Anginazol; Angisan; Citropain nouvelle formule; Gem nouvelle formule contre le mal de gorge; Hextriletten†; Hextrimint†; Impuls†; Lidazon Actilong; Lidazon; Lysopaine N; Mebucaine; Neo-Angin; Otothricinol; Pastilles contre le mal de gorge†; Rotpunkt Apotheke nouvelle formule pastilles contre le mal de gorge†; Swidro nouvelle formule pastilles contre le mal de gorge†; Zurcher Bahnhof Apotheke pastilles contre le mal de gorge nouvelle formule†; *Thai.*: Sentril†; Sore Mouth Gel†; *Turk.*: Calgel; Garol; Nesgarin; Sorbeks; *UAE*: B-Cool; New BCool; *UK*: Adult Meltus for Chesty Coughs & Catarrh; Allens Dry Tickly Cough; Anbesol; Bonjela Junior; Calgel; Dentinox Teething Gel; Kilkof; Listermint with Fluoride; Macleans Mouthguard; Meltus Expectorant; Meltus Junior Expectorant; Merocaine; Merocets Plus; Rinstead; Woodwards Teething Gel; *Ukr.*: Grammidin Neo (Граммидин Нео); Grammidin with Anaesthetic Neo (Граммидин С Анестетиком Нео); Septolete Plus (Септолете Плюс); *USA*: Cepacol Maximum Strength Sore Throat†; Cylex; MouthKote O/R; Orajel Mouth Aid; Orasep; *Venez.*: Borogin; Cepacol BE; Isospray; Lafarcaina; Solunovar Compuesto.

Pharmacopoeial Preparations

USP 36: Cetylpyridinium Chloride Lozenges; Cetylpyridinium Chloride Topical Solution.

Chlorhexidine *(BAN, rINN)*

Chlorhexidinum; Clorhexidina; Klooriheksidiini; Klorheksidin; Klorhexidin; Хлорексидин.

CAS — 55-56-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — R4KO0DY52L.

Chlorhexidine Acetate *(BANM, rINNM)*

Acetato de clorhexidina; Chlorheksidino diacetatas; Chlorhexidindiacetát; Chlorhexidin-diacetát; Chlorhexidine, Acétate de; Chlorhexidine Diacetate; Chlorhexidiné, diacétate de; Chlorhexidini Acetas; Chlorhexidini Diacetas; Chloroheksydyny octan; Clorhexidina, acetato de; Kloorheksidiinidiasetaatti; Klorhexidindiacetat; Klórhexidin-diacetát; Хлорексидина Ацетат.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] diacetate.

$C_{22}H_{30}Cl_2N_{10}.2C_2H_4O_2$=625.6

CAS — 56-95-1.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — 590BZUF22Y.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Chlorhexidine Diacetate). A white or almost white, microcrystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycol.

USP 36: (Chlorhexidine Acetate). A white or almost white, microcrystalline powder. Sparingly soluble in water; soluble in alcohol; slightly soluble in glycerol and in propylene glycerol. Protect from light.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, p. 1744.1.

Chlorhexidine Gluconate *(BANM, USAN, rINNM)*

Chlorheksidino digliukonato tirpalas; Chlorhexidin-digluconát; Chlorhexidine Digluconate; Chlorhexidine, digluconate de; Chlorhexidine, Gluconate de; Chlorhexidini digluconas; Chlorhexidini Digluconatis Solutio; Chlorheksidini Glukonas; Chloroheksydyny diglukonianu roztwór; Clorhexidina, gluconato de; Gluconato de clorhexidina; Kloorheksidiinidiglukonaattiliuos; Klorheksidin Glukonat; Klorhexidindiglukonatlösning; Klórhexidin-diglükónát-oldat; Хлоргексидина Глюконат.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] digluconate.

$C_{22}H_{30}Cl_2N_{10}.2C_6H_{12}O_7$=897.8

CAS — 18472-51-0.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — MOR84MUD8E.

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US* include a solution which contains 19 to 21% of chlorhexidine gluconate.

Ph. Eur. 8: (Chlorhexidine Digluconate Solution; Chlorhexidini Digluconatis Solutio; Chlorhexidine Gluconate Solution BP 2014). An aqueous solution which contains not less than 190 g/litre and not more than 210 g/litre of chlorhexidine gluconate. An almost colourless or pale-yellowish liquid. Miscible with water, with not more than 5 parts of alcohol, and with not more than 3 parts of acetone. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Protect from light.

USP 36: (Chlorhexidine Gluconate Solution). An aqueous solution which contains not less than 19% and not more than 21% of chlorhexidine gluconate. An almost colourless or pale yellow, clear liquid. Miscible with water and with glacial acetic acid; miscible with five times its volume of dehydrated alcohol and with three times its volume of acetone; further addition of dehydrated alcohol or of acetone yields a white turbidity. A 5% v/v dilution in water has a pH of 5.5 to 7.0. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of chlorhexidine salts are discussed under Chlorhexidine Hydrochloride, below.

Stability. The stability of chlorhexidine salts is discussed under Chlorhexidine Hydrochloride, p. 1744.1.

Sterilisation. Dilutions of commercial concentrated solutions may be sterilised by autoclaving.

Chlorhexidine Hydrochloride

(BANM, USAN, rINNM)

AY-5312; Chlorheksidino dihidrochloridas; Chlorhexidindihydrochlorid; Chlorhexidindihydrochlorid; Chlorhexidine, Chlorhydrate de; Chlorhexidine, dichlorhydrate de; Chlorhexidine Dihydrochloride; Chlorhexidini Dihydrochloridum; Chlorhexidini Hydrochloridum; Clorhexidina, hidrocloruro de; Hidrocloruro de clorhexidina; Kloorheksidiinidihydrokloridi; Klorheksidin Hidroklorür; Klórhexidin-dihidroklorid; Klorhexidindihydroklorid; Хлоргексидина Гидрохлорид.

1,1′-Hexamethylenebis[5-(4-chlorophenyl)biguanide] dihydrochloride.

$C_{22}H_{30}Cl_2N_{10}.2HCl$=578.4

CAS — 3697-42-5.

ATC — A01AB03; B05CA02; D08AC02; D09AA12; R02AA05; S01AX09; S02AA09; S03AA04.

ATC Vet — QA01AB03; QB05CA02; QD08AC02; QD09AA12; QR02AA05; QS01AX09; QS02AA09; QS03AA04.

UNII — E64XL9U38K.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US.*

Ph. Eur. 8: (Chlorhexidine Dihydrochloride; Chlorhexidine Hydrochloride BP 2014). A white or almost white, crystalline powder. Sparingly soluble in water and in propylene glycol; very slightly soluble in alcohol.

USP 36: (Chlorhexidine Hydrochloride). A white or almost white, crystalline powder. Sparingly soluble in water and in propylene glycol; very slightly soluble in alcohol. Protect from light.

Incompatibility. Chlorhexidine salts are incompatible with soaps and other anionic materials. Activity may be reduced in the presence of suspending agents such as alginates and tragacanth, insoluble powders such as kaolin, and insoluble compounds of calcium, magnesium, and zinc. Chlorhexidine acetate is incompatible with potassium iodide. At a concentration of 0.05%, chlorhexidine salts are incompatible with borates, bicarbonates, carbonates,

chlorides, citrates, nitrates, phosphates, and sulfates, forming salts of low solubility which may precipitate out of solution. At dilutions of 0.01% or more, these salts are generally soluble. Insoluble salts may form in hard water. Chlorhexidine salts are inactivated by cork.

References to incompatibilities of chlorhexidine with suspending agents and insoluble solids.[1-3]

1. McCarthy TJ. The influence of insoluble powders on preservatives in solution. *J Mond Pharm* 1969; 12: 321–8.
2. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; 8: 54–6.
3. McCarthy TJ, Myburgh JA. The effect of tragacanth gel on preservative activity. *Pharm Weekbl* 1974; 109: 265–8.

Stability. Chlorhexidine and its salts are stable at normal storage temperatures but when heated may decompose with the production of trace amounts of 4-chloroaniline. Chlorhexidine hydrochloride is less readily decomposed than chlorhexidine acetate and may be heated at 150 degrees for 1 hour without appreciable production of 4-chloroaniline. Aqueous solutions of chlorhexidine salts decompose with the formation of trace amounts of 4-chloroaniline. This decomposition is increased by heating and alkaline pH.

Uses and Administration

Chlorhexidine is a bisbiguanide antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of Gram-positive and Gram-negative bacteria. It is more effective against Gram-positive than Gram-negative bacteria, and some species of *Pseudomonas* and *Proteus* have low susceptibility. It is relatively ineffective against mycobacteria. Chlorhexidine inhibits some viruses and is active against some fungi. It is inactive against bacterial spores at room temperature. Chlorhexidine is most active at a neutral or slightly acid pH. Combinations of chlorhexidine with cetrimide (p. 1742.1) or in alcoholic solution are used to enhance efficacy.

Chlorhexidine is formulated as lotions, washes, and creams for disinfection and cleansing of skin and wounds (p. 1690.1), and as oral gels, sprays, and mouthwashes for mouth infections including candidiasis and to reduce dental plaque accumulation. It has also been used with neomycin to eliminate nasal carriage of staphylococci (p. 208.2) and for disinfection of some contact lenses (but see Precautions, p. 1745.3). It has been suggested for use with propamidine isetionate for the treatment of Acanthamoeba keratitis and in spermicides to prevent transmission of HIV infection (see HIV Infection Prophylaxis, p. 959.1).

For pre-operative skin disinfection and hand-washing, chlorhexidine is used as a 0.5% solution of the acetate or gluconate in alcohol (70%) or as a 2 or 4% detergent solution of the gluconate. For disinfection of wounds, burns, or other skin damage or disorders chlorhexidine is used as a 0.05% aqueous solution of the acetate or gluconate, as a tulle dressing impregnated with chlorhexidine acetate 0.5%, or as a cream or powder containing chlorhexidine acetate or gluconate 1%. Preparations containing chlorhexidine acetate or gluconate 0.015% and cetrimide 0.15% are also used for cleansing and disinfection of skin and wounds. In obstetrics, chlorhexidine gluconate is used as a 0.05% aqueous solution or a 1% cream. The cream is also used as a barrier against bacterial hand infection.

Chlorhexidine gluconate is used in a 1% dental gel, 0.2% oral spray, and 0.1 to 0.2% mouthwash for the prevention of plaque and the prevention and treatment of gingivitis and in the treatment of oral candidiasis. A slow-release formulation containing 2.5 mg of chlorhexidine gluconate for insertion into periodontal pockets is also available.

A 0.02% solution may be used as a bladder irrigation in some urinary-tract infections. A gel containing 0.25% chlorhexidine gluconate solution and lidocaine hydrochloride has been used in catheterisation and cystoscopy.

For the emergency disinfection of clean instruments, a 2-minute immersion in chlorhexidine acetate or gluconate 0.5% in alcohol (70%) is used; for the storage and disinfection of clean instruments a 30-minute immersion in a 0.05% aqueous solution containing 0.1% sodium nitrite to inhibit metal corrosion is used.

As an antimicrobial preservative, chlorhexidine is used at a concentration of 0.01% of the acetate or gluconate in eye drops. Solutions containing 0.002 to 0.006% of chlorhexidine gluconate have also been used for disinfection of hydrophilic contact lenses.

Acanthamoeba infections. As discussed on p. 919.3, the optimal antiamoebic therapy for *Acanthamoeba* keratitis has yet to be determined. Propamidine isetionate is commonly used, usually in combinations including a biguanide. A multicentre study[1] evaluated the efficacy of a combination of topical chlorhexidine 0.02% and propamidine 0.1% in 12 contact lens-wearing patients with confirmed *Acanthamoeba* keratitis. Patients were treated for between 2 to 6 months and resolution of signs occurred gradually over 5 to 28 weeks (mean 11 weeks). Resolution of symptoms occurred within 1 to 7 weeks (mean 3 weeks); patients noted a reduction of pain, photophobia and lid oedema after 3 weeks of treatment. No drug toxicity was noted in any of the patients. However, concern has been expressed over the possible toxicity of chlorhexidine at this concentration on the cornea (see Adverse Effects and Treatment, p. 1745.1).

Chlorhexidine is also an effective disinfectant against *Acanthamoeba* cysts and most bacteria found in contact lens storage cases.[2]

Chlorhexidine has also been used to treat skin lesions associated with disseminated *Acanthamoeba* infection[3] as an adjunct to systemic therapy (see p. 920.1).

1. Seal D, *et al.* Successful medical therapy of Acanthamoeba keratitis with topical chlorhexidine and propamidine. *Eye* 1996; 10: 413–21.
2. Seal DV. Acanthamoeba keratitis. *BMJ* 1994; 308: 1116–17.
3. Slater CA, *et al.* Brief report: successful treatment of disseminated Acanthamoeba infection in an immunocompromised patient. *N Engl J Med* 1994; 331: 85–7.

Contraception. Bisbiguanides of the chlorhexidine type are reported to have the ability to diffuse into cervical mucus and render it impenetrable to sperm at concentrations as low as 1 mg/mL.[1] Higher concentrations of chlorhexidine structurally modify the mucus, producing a barrier to both the entry of sperm and chlorhexidine. The potency[1] of chlorhexidine in inhibiting sperm motility *in vitro* is identical to that of nonoxinol 9, but unlike spermicides containing nonoxinol 9, which tend to trickle out, the clearance of chlorhexidine from the vagina is delayed.[2] Chlorhexidine also has potential for reducing transmission of HIV infection as it does not disrupt the vaginal epithelium and has activity *in vitro* against the HIV virus in low concentrations.[2]

For a review of contraception, including the view that spermicides are not a particularly effective method unless used with other means of contraception, see p. 2232.3.

1. Pearson RM. Update on vaginal spermicides. *Pharm J* 1985; 234: 686–7.
2. Anonymous. Multipurpose spermicides. *Lancet* 1992; 340: 211–13.

Disinfection. Viable bacterial counts on the hands were reduced by a mean of 97.9% by the application of chlorhexidine gluconate 0.5% in alcohol 95%.[1] The reduction was not so substantial with a 0.5% chlorhexidine aqueous solution (65.1% reduction in bacterial count) or a 4% detergent solution (86.7%). Hand disinfection with chlorhexidine gluconate 4% appeared to be more effective than the use of isopropyl alcohol 60% and soap in preventing nosocomial infections in a study conducted in intensive care units but this may have been partly due to better compliance with hand-washing instructions when using chlorhexidine.[2] In another study,[3] pre-operative total body bathing with a 4% detergent did not decrease the risk of wound infection in patients compared with bathing in detergent alone.

Chlorhexidine 1% nasal cream failed to control an epidemic of meticillin-resistant *Staphylococcus aureus* in a neurosurgical ward[4] and handwashing with chlorhexidine soap failed to control an outbreak of infection with *Staph. aureus* resistant to meticillin and gentamicin in a neonatal intensive care unit.[5] The organisms were subsequently eradicated by the use of nasal mupirocin and hexachlorophene handwashing, respectively.

1. Lowbury EJL, *et al.* Preoperative disinfection of surgeons' hands: use of alcoholic solutions and effects of gloves on skin flora. *BMJ* 1974; 4: 369–72.
2. Doebbeling BN, *et al.* Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. *N Engl J Med* 1992; 327: 88–93.
3. The European Working Party on Control of Hospital Infections. A comparison of the effects of preoperative whole-body bathing with detergent alone and with detergent containing chlorhexidine gluconate on the frequency of wound infections after clean surgery. *J Hosp Infect* 1988; 11: 310–20.
4. Duckworth G. New method for typing Staphylococcus aureus resistant to methicillin. *BMJ* 1986; 293: 885.
5. Reboli AC, *et al.* Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; 143: 34–9.

INJECTION SITE AND CATHETER CARE. See p. 1732.1.

Endocarditis. Some guidelines[1] have recommended chlorhexidine mouthwash 0.2%, held in the mouth for 1 minute, as an adjunct to antimicrobials for the prophylaxis of endocarditis in at-risk patients undergoing dental procedures; however, subsequent guidelines[2,3] consider topical antiseptic rinses to be ineffective for such use and recommend that they should not be used. The protective cover required for such patients is discussed on p. 179.2.

1. Gould FK, *et al.* Guidelines for the prevention of endocarditis: report of the Working Party of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother* 2006; 57: 1035–42. Also available at: http://jac.oxfordjournals.org/cgi/reprint/dkl121v1.pdf (accessed 23/06/10)
2. Wilson W, *et al.* Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* 2007; 116: 1736–54. Also available at: http://circ.ahajournals.org/cgi/reprint/116/15/1736.pdf (accessed 23/06/10)
3. NICE. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (issued March 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/CG64NICEguidance.pdf (accessed 23/06/10)

Mouth disorders. Chlorhexidine mouthwashes, sprays, and gels are used to prevent accumulation of dental plaque (see Mouth Infections, p. 192.3). Early studies[1-4] generally showed chlorhexidine mouthwash 0.1 to 0.2% used 2 or 3 times daily to be effective in reducing plaque accumulation and gingivitis and provided limited evidence of efficacy in preventing caries in permanent teeth of children and adolescents. A retrospective review[5] of 22 controlled studies of chlorhexidine for caries prevention, found the evidence inconclusive in schoolchildren and adolescents with active caries and regular fluoride exposure; there was also no good evidence that it arrested root caries in patients with dry mouth and in frail elderly subjects. However, chlorhexidine varnishes showed a preventative effect for fissure caries compared with no treatment in children with low fluoride exposure. Other studies have shown that chlorhexidine reduces gingivitis by 60 to 90% but its use is limited by its unpleasant taste and staining properties; special circumstances in which chlorhexidine is helpful include management of acute gingivitis, control of periodontal involvement in immunocompromised patients, and promotion of healing after periodontal treatment.[6]

Chlorhexidine gluconate may be useful in controlling secondary bacterial infections of aphthous ulcers (see Mouth Ulceration, p. 1811.2). Local application of chlorhexidine has been reported to reduce the incidence[7] and duration and severity[8] of recurrent ulcers, although one study showed no benefit compared with placebo.[9] However, a retrospective review[10] of 7 studies comparing chlorhexidine with placebo or no treatment found no evidence that chlorhexidine prevents oral mucositis in patients receiving cancer treatment.

Chlorhexidine may be a useful adjunct to antifungal treatment of oral candidiasis[11] (p. 564.1).

For the need for a delay when using chlorhexidine with other oral hygiene preparations, see under Precautions, p. 1745.3.

1. Flötra L, *et al.* A 4-month study on the effect of chlorhexidine mouth washes on 50 soldiers. *Scand J Dent Res* 1972; 80: 10–17.
2. O'Neil TCA, Figures KH. The effects of chlorhexidine and mechanical methods of plaque control on the recurrence of gingival hyperplasia in young patients taking phenytoin. *Br Dent J* 1982; 152: 130–3.
3. de la Rosa M, *et al.* The use of chlorhexidine in the management of gingivitis in children. *J Periodontol* 1988; 59: 387–9.
4. O'Neil TCA. The use of chlorhexidine mouthwash in the control of gingival inflammation. *Br Dent J* 1976; 141: 276–80.
5. Tweuman S. Antimicrobials in future caries control: a review with special reference to chlorhexidine treatment. *Caries Res* 2004; 38: 223–9.
6. Greene JC, *et al.* Preventive dentistry II: periodontal diseases, malocclusion, trauma, and oral cancer. *JAMA* 1990; 263: 421–5.
7. Hunter L, Addy M. Chlorhexidine gluconate mouthwash in the management of minor aphthous ulceration. *Br Dent J* 1987; 162: 106–10.
8. Addy M, *et al.* Management of recurrent aphthous ulceration: a trial of chlorhexidine gluconate gel. *Br Dent J* 1976; 141: 118–20.
9. Matthews RW, *et al.* Clinical evaluation of benzydamine, chlorhexidine, and placebo mouthwashes in the management of recurrent aphthous stomatitis. *Oral Surg Oral Med Oral Pathol* 1987; 63: 189–91.
10. Worthington HV, *et al.* Interventions for preventing oral mucositis for patients with cancer receiving treatment. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2007 (accessed 27/08/08).
11. WHO. *WHO model prescribing information: drugs used in skin diseases.* Geneva: WHO, 1997.

Obstetric use. Disinfection of the birth canal with chlorhexidine gluconate 0.05 to 0.4% during labour has been investigated as a method for reducing mother-to-child transmission of infections, including early-onset group B streptococcal infection and HIV.[1-6] Studies have shown that it has not reduced perinatal transmission of HIV except when membranes were ruptured for more than 4 hours before delivery[1] or if used before the membranes rupture and at higher concentrations.[4] A systematic review of 5 studies[5] to determine the efficacy of chlorhexidine vaginal disinfection for preventing early-onset group B streptococcal infection concluded that, although there was a statistically significant reduction in colonisation there was no significant reduction in early-onset infection, morbidity or mortality. Comparable results have been reported with the use of chlorhexidine gluconate 1% obstetric cream at each examination during labour.[3] Similarly, a large randomised controlled study assessing intrapartum and neonatal use of chlorhexidine 0.5%, concluded there was no effect on neonatal sepsis,[7] although it has been argued that this simple intervention should not be abandoned.[8]

A systematic review of 3 studies[6] to determine the efficacy of chlorhexidine vaginal disinfection for preventing perinatal transmission of infections other than group B streptococcal infection and HIV found no evidence to support its use. However, a study[2] conducted in Malawi

reported a reduction in neonatal morbidity and mortality from other neonatal infections.

1. Biggar RJ, *et al.* Perinatal intervention trial in Africa: effect of a birth canal cleansing intervention to prevent HIV transmission. *Lancet* 1996; 347: 1647–50.
2. Taha TE, *et al.* Effect of cleansing the birth canal with antiseptic solution on maternal and newborn morbidity and mortality in Malawi: clinical trial. *BMJ* 1997; 315: 216–20.
3. Lindemann R, *et al.* Vaginal chlorhexidine disinfection during labour. *Lancet* 1992; 340: 792.
4. Gaillard P, *et al.* Vaginal lavage with chlorhexidine during labour to reduce mother-to-child HIV transmission: clinical trial in Mombasa, Kenya. *AIDS* 2001; 15: 389–96.
5. Slade B, *et al.* Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2004 (accessed 06/04/10).
6. Lumbiganon P, *et al.* Vaginal chlorhexidine during labour for preventing maternal and neonatal infections (excluding group B streptococcal and HIV). Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2004 (accessed 06/04/10).
7. Cutland CL, *et al.* PoPS Trial Team. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. *Lancet* 2009; 374: 1909–16.
8. Mullany LC, Biggar RJ. Vaginal and neonatal skin cleansing with chlorhexidine. *Lancet* 2009; 374: 1873–3.

Urinary catheter-related infection. Chlorhexidine solutions have been used in the management of catheter-related bladder infections and for urinary catheter maintenance. Twice-daily bladder irrigation with chlorhexidine acetate 0.02% did not produce a reduction in urinary bacterial counts in geriatric patients with indwelling catheters, and there was a tendency for overgrowth of *Proteus* spp. in patients given chlorhexidine.[1] In patients undergoing prostatectomy, intermittent pre-operative bladder irrigation with chlorhexidine gluconate 0.05% reduced the incidence of bacteraemia and severe wound infection, although urinary infections were eradicated in only 3 of the 13 patients treated.[2]

Addition of chlorhexidine to catheter drainage bags was not shown to reduce the frequency of urinary infections,[3] but infection rates were reduced by combining this technique with the use of a catheter lubricant containing chlorhexidine, disinfection of the urethral meatus, and aseptic nursing procedures.[4] The use of lubricating gel containing chlorhexidine did not reduce the risk of urinary-tract infections associated with short-term catheterisation,[5] and in general external disinfection of the periurethral area alone does not seem to be of benefit in reducing the rate of catheter-related bacteriuria.[6,7]

The treatment of urinary-tract infections is discussed on p. 213.1.

1. Davies AJ, *et al.* Does instillation of chlorhexidine into the bladder of catheterized geriatric patients help reduce bacteriuria? *J Hosp Infect* 1987; 9: 72–5.
2. Adesanya AA, *et al.* The use of intermittent chlorhexidine bladder irrigation in the prevention of post-prostatectomy infective complications. *Int Urol Nephrol* 1993; 25: 359–67.
3. Gillespie WA, *et al.* Does the addition of disinfectant to urine drainage bags prevent infection in catheterised patients? *Lancet* 1983; i: 1037–9.
4. Southampton Infection Control Team. Evaluation of aseptic techniques and chlorhexidine on the rate of catheter-associated urinary-tract infection. *Lancet* 1982; i: 89–91.
5. Schiotz HA. Antiseptic catheter gel and urinary tract infection after short-term postoperative catheterization in women. *Arch Gynecol Obstet* 1996; 258: 97–100.
6. Webster J, *et al.* Water or antiseptic for periurethral cleaning before urinary catheterization: a randomized controlled trial. *Am J Infect Control* 2001; 29: 389–94.
7. Koskeroglu N, *et al.* The role of meatal disinfection in preventing catheter-related bacteriuria in an intensive care unit: a pilot study in Turkey. *J Hosp Infect* 2004; 56: 236–8.

Adverse Effects and Treatment

Skin sensitivity to chlorhexidine has occasionally been reported. Severe hypersensitivity reactions, including anaphylactic shock, have been reported rarely after topical use of chlorhexidine. Strong solutions may cause irritation of the conjunctiva and mucous membranes. The use of chlorhexidine dental gel and mouthwash has been associated with reversible discoloration of the tongue, teeth, and silicate or composite dental restorations. Transient taste disturbances and a burning sensation of the tongue may occur on initial use. Oral desquamation and occasional parotid gland swelling have been reported with the mouthwash. If desquamation occurs, 50% dilution of the mouthwash with water and less vigorous rinsing may allow continued use.

The main consequence of ingestion is mucosal irritation and systemic toxicity is rare due to minimal absorption from the gastrointestinal tract (see Poisoning, below). Haemolysis has been reported after accidental intravenous administration. Gastric lavage with demulcents has been suggested in some licensed product information for treatment of acute ingestion; however, other authorities recommend that the stomach should not be emptied as this may increase the risk of mucosal irritation. Small volumes of milk or water to drink may be warranted.

Effects on the eyes. Corneal damage was reported in 4 patients after use of chlorhexidine gluconate for pre-operative preparation of facial skin.[1] Severe corneal endothelium damage occurred in a further 3 patients[2] when chlorhexidine was inadvertently used as an intra-ocular irrigating solution and 2 of the patients subsequently required penetrating keratoplasty. Other adverse effects included pronounced iris atrophy, anterior chamber flattening, and a retrocorneal membrane; one patient developed raised intra-ocular pressure. In another case progressive ulcerative keratitis and almost total loss of the corneal epithelium was reported[3] after use of chlorhexidine gluconate 0.02% and propamidine 0.1% eye drops for 8 weeks for *Acanthamoeba* keratitis. In 2 patients[4] treated similarly for 4 to 6 months, deep marginal ulceration of the cornea developed, in each case requiring a penetrating graft; a mature cataract and an atrophic iris were seen in each patient after removal of the cornea. Due to the similarity of both cases, it was suggested that these complications were caused by the drugs rather than by amoeba-induced inflammation.

1. Tabor E, *et al.* Corneal damage due to eye contact with chlorhexidine gluconate. *JAMA* 1989; 261: 557–8.
2. Anders N, Wollensak J. Inadvertent use of chlorhexidine instead of balanced salt solution for intraocular irrigation. *J Cataract Refract Surg* 1997; 23: 959–62.
3. Murthy S, *et al.* Progressive ulcerative keratitis related to the use of topical chlorhexidine gluconate (0.02%). *Cornea* 2002; 21: 237–9.
4. Ehlers N, Hjortdal J. Are cataract and iris atrophy toxic complications of medical treatment of acanthamoeba keratitis? *Acta Ophthalmol Scand* 2004; 82: 228–31.

Effects on the nose. Temporary hyposmia (reduced sense of smell) in some patients after transsphenoidal pituitary adenoma operation was assumed to be caused by pre-operative disinfection of the nasal cavity with chlorhexidine gluconate solution.[1]

1. Yamagishi M, *et al.* Impairment of olfactory epithelium treated with chlorhexidine digluconate (Hibitane). *Pract Otol* 1985; 78: 399–409.

Hypersensitivity. Both immediate and delayed hypersensitivity reactions have been reported after topical use of chlorhexidine[1] and from the use of chlorhexidine-containing urethral lubricants.[2] However, the incidence is low given the frequent use of chlorhexidine. Delayed hypersensitivity reactions such as contact dermatitis, fixed drug eruptions, and photosensitivity reactions are more common than immediate hypersensitivity reactions (acute urticaria, angioedema, and bronchospasm which may progress to anaphylactic shock).[1,3]

Immediate hypersensitivity reactions have also occurred with surgical disinfection. Signs appear 15 to 45 minutes after the start of surgery and include hypotension, urticaria, tachycardia, bronchospasm, and sometimes anaphylactic shock, cardiovascular collapse, or cardiac arrest.[3,4] In 1998 the FDA issued a public notice[5] warning of potential hypersensitivity reactions to chlorhexidine-impregnated intravenous catheters, topical antimicrobial skin dressings, and implanted antimicrobial surgical mesh, based on reports of adverse events that had occurred in the USA and other countries.

Occupational asthma has been attributed to an alcoholic chlorhexidine spray.[6]

1. Krautheim AB, *et al.* Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004; 50: 113–16.
2. Jayathillake A, *et al.* Allergy to chlorhexidine gluconate in urethral gel: report of four cases and review of the literature. *Urology* 2003; 61: 837iv–837vi.
3. Beaudouin E, *et al.* Immediate hypersensitivity to chlorhexidine: literature review. *Allerg Immunol (Paris)* 2004; 36: 123–6.
4. Chisholm DG, *et al.* Intranasal chlorhexidine resulting in an anaphylactic circulatory arrest. *BMJ* 1997; 315: 785.
5. FDA. FDA Public Health notice potential hypersensitivity reactions to chlorhexidine-impregnated medical devices (issued 11th March, 1998). Available at: http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/UCM062306 (accessed 11/05/10)
6. Waclawski ER, *et al.* Occupational asthma in nurses caused by chlorhexidine and alcohol aerosols. *BMJ* 1989; 298: 929–30.

Poisoning. Reports of adverse effects after *ingestion* of chlorhexidine salts include a neonate who developed multiple episodes of cyanosis and bradycardia;[1] the infant's mother had sprayed chlorhexidine onto her breasts to prevent mastitis. In contrast an 89-year-old woman only had mild giddiness, unusual laughter, and an increased appetite after mistakenly drinking 30 mL of a solution containing chlorhexidine gluconate 4% and isopropyl alcohol 4%.[2] A review[3] of 7 adult cases of deliberate ingestion of a commercially available mixture of cetrimide 3% and chlorhexidine gluconate 0.3%, concluded that symptoms were generally mild and included nausea, vomiting, sore throat, and abdominal pain. There has also been a report of a patient who developed gastritis after ingesting a pre-operative skin preparation containing chlorhexidine gluconate 4% when using it as a mouthwash.[4]

Another person had much more serious effects after drinking about 150 mL of chlorhexidine gluconate solution, corresponding to about 30 g of the pure substance.[5] Besides pharyngeal oedema and necrotic oesophageal lesions, the patient had aminotransferase concentrations that rose to 30 times normal 5 days after ingestion and were still 8 times normal one week later. After one month the serum aspartate aminotransferase was returning to normal while the serum alanine aminotransferase was still 3 times normal. Six months after ingestion the aminotransferase levels were normal. A liver biopsy performed soon after the peak in aminotransferase levels showed diffuse fatty degeneration and lobular hepatitis suggesting that chlorhexidine was absorbed from the gastrointestinal tract in a concentration high enough to produce liver necrosis. An 80-year-old woman had spontaneous vomiting and aspiration followed by acute respiratory distress syndrome within 5 hours of accidental ingestion of 200 mL of a chlorhexidine gluconate 5% solution.[6] Despite supportive treatment, the patient's condition continued to deteriorate and she developed shock and metabolic acidosis and died from cardiac arrest 12 hours after ingestion.

Accidental ***intravenous*** administration of 4 mL of a 20% chlorhexidine gluconate solution in a 67-year-old man undergoing a colectomy resulted in the sudden development of acute respiratory distress syndrome.[7] Respiratory failure progressed despite plasma exchange therapy over 3 consecutive days. Veno-arterial extracorporeal membrane oxygenation was started on the third day and after 72 hours improvement was noted and the patient subsequently recovered completely.

1. Quinn MW, Bini RM. Bradycardia associated with chlorhexidine spray. *Arch Dis Child* 1989; 64: 892–3.
2. Emerson D, Pierce C. A case of a single ingestion of 4% Hibiclens. *Vet Hum Toxicol* 1988; 30: 583.
3. Chan TYK. Poisoning due to Savlon (cetrimide) liquid. *Hum Exp Toxicol* 1994; 13: 681–2.
4. Roche S, *et al.* Chlorhexidine-induced gastritis. *Postgrad Med J* 1991; 67: 210–11.
5. Massano G, *et al.* Striking aminotransferase rise after chlorhexidine self-poisoning. *Lancet* 1982; i: 289.
6. Hirata K, Kurokawa A. Chlorhexidine gluconate ingestion resulting in fatal respiratory distress syndrome. *Vet Hum Toxicol* 2002; 44: 89–91.
7. Ishigami S, *et al.* Intravenous chlorhexidine gluconate causing acute respiratory distress syndrome. *J Toxicol Clin Toxicol* 2001; 39: 77–80.

Precautions

Since chlorhexidine is irritant it is recommended that it should not be used on the brain, meninges, middle ear, or other sensitive tissues. Contact with the eye should be avoided except for dilute solutions expressly for use in the eyes. Chlorhexidine may be adsorbed by some soft contact lenses and cause eye irritation, although it may be suitable for use with others (see Contact Lens Care, p. 1730.2). Syringes and needles that have been immersed in chlorhexidine solutions should be thoroughly rinsed with sterile water or saline before use.

Aqueous solutions of chlorhexidine salts may be susceptible to contamination with micro-organisms. To reduce this risk, a sterilised preparation should be used or, where necessary, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Aqueous solutions of chlorhexidine used for instrument storage should contain sodium nitrite 0.1% to inhibit metal corrosion, and should be changed every 7 days. Commercial 5% concentrate contains a nonionic surfactant to prevent precipitation on dilution with hard water and is not suitable for use in body cavities or for disinfection of instruments containing cemented glass components; dilutions of the 20% concentrate should be used for this purpose.

Contamination. *Ralstonia pickettii* (*Burkholderia pickettii*; *Pseudomonas pickettii*) septicaemia developed in 6 patients after the use of aqueous chlorhexidine 0.05%, prepared with contaminated twice-distilled water, for skin disinfection before venepuncture and it was considered that unsterilised 0.05% solutions should not be used for such skin preparation.[1] Positive blood cultures of *Burkholderia cepacia* (*Pseudomonas cepacia*) were found in 2 patients after inappropriate use of a chlorhexidine handwash for the same purpose.[2] Further studies showed that the handwash supported pseudomonal growth only when diluted.[3]

1. Kaban A, *et al.* Is chlorhexidine an essential drug? *Lancet* 1984; ii: 759–60.
2. Gosden PE, Norman P. Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1985; ii 671–2.
3. Norman P, *et al.* Pseudobacteraemia associated with contaminated skin cleansing agent. *Lancet* 1986; i: 209.

Neonates. Haemorrhagic skin necrosis associated with umbilical artery catheterisation in a premature infant was attributed to damage by the alcohol from the use of chlorhexidine 0.5% in spirit 70% as a disinfectant.[1]

For reference to the percutaneous absorption of chlorhexidine after topical use in neonates and infants, see under Pharmacokinetics, p. 1746.1.

1. Harpin V, Rutter N. Percutaneous alcohol absorption and skin necrosis in a preterm infant. *Arch Dis Child* 1982; 57: 477–9.

Oral hygiene. Toothpastes may contain anionic surfactants such as sodium laurilsulfate, which are incompatible with chlorhexidine. In order that the antiplaque effect of

chlorhexidine is not reduced, it has been recommended that at least 30 minutes should be allowed to elapse between teeth brushing and rinsing with oral chlorhexidine preparations.[1]

1. Barkvoll P, *et al.* Interaction between chlorhexidine digluconate and sodium lauryl sulfate in vivo. *J Clin Periodontol* 1989; 16: 593–5.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies chlorhexidine as not porphyrinogenic: it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Washing precautions. Fabrics that have been in contact with chlorhexidine solution may develop a brown stain if bleached with a hypochlorite. A peroxide bleach may be used instead.

Pharmacokinetics

Chlorhexidine is poorly absorbed from the gastrointestinal tract and skin.

Neonates. Occasional reports of the percutaneous absorption of chlorhexidine in neonates and infants include a study in which chlorhexidine was detected in low concentrations in the venous blood of 5 of 24 infants after washing them with a preparation containing chlorhexidine gluconate 4% (*Hibiscrub*); no adverse effects were noted.[1] Low concentrations have been found[2] in the venous blood of neonates after the topical use of a powder containing chlorhexidine 1%. Percutaneous absorption of chlorhexidine was reported in preterm neonates (but not full-term infants) treated with chlorhexidine 1% in alcohol for neonatal cord care; no such absorption occurred when a dusting powder containing chlorhexidine 1% and zinc oxide 3% was used.[3]

1. Cowen J, *et al.* Absorption of chlorhexidine from the intact skin of newborn infants. *Arch Dis Child* 1979; 54: 379–83.
2. Alder VG, *et al.* Comparison of hexachlorophane and chlorhexidine powders in prevention of neonatal infection. *Arch Dis Child* 1980; 55: 277–80.
3. Aggett PJ, *et al.* Percutaneous absorption of chlorhexidine in neonatal cord care. *Arch Dis Child* 1981; 56: 878–91.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Acipoun; Antiminth; Biguanex; Bucogel; Elugel; Finaplac†; Hexidin†; Hexil-P; Hexil†; Hibiscot; Hibiscrub; Laclorhex; Periodil; Pervinox Clorhexidina; Pervinox Incoloro; Plac Out; *Austral.*: Bactigras; Catheter Preparation†; Microshield; Periogard Chlorohex†; Plaqcide; Savacol Mouth and Throat Rinse; *Austria*: Chlorhexamed; *Belg.*: Astrexine; Baxil; Cedium Chlorhexidine; Cedixidin; Corsodyl; Golaseptine; Hansamedic†; Hibidil; Hibiguard†; Hibiscrub; Hibitane; Hibitane; Medisepta; Medixidin; Mefren; Mefren; Pixidin; Sterilon†; Uro-Tainer; *Braz.*: Asseptcare; Asseptic Hibitane; Marclorhex; Merthiodean; Noplak†; *Canad.*: Antiseptic Cleanser; Antiseptic First Aid; Antiseptic Skin Cleanser; Bactigras†; Baxedin; Bioson; Biovac Chlorhexseptic; Clean Derm; Endure Cida; Endure Scrub; First Aid Antiseptic Skin Cleanser; Germi Stat; Hibidil†; Hibitane; Oro-Clense; Oronine H†; Perichlor; Peridex; Periogard; Prevora 1; Provon Antiseptic Soft Care CHG Antimicrobial; Solu-IV CHG; Solunet C; Solunet Mousse; Soluprep; Spectro Gram†; Stanhexidine; Sterixin; Tegaderm CHG; Vap; *Chile*: AB; Bucoseptil; Dentilim; Elugel; Freshmel; Garonsept†; Graneodin; Oralgene; Ortoxine; Perio-Aid; Periokin†; *China*: Jiu Tai (九泰); Kou Tai (口泰); Ya Nuo (雅诺); *Cz.*: Corsodyl; Septofort; *Denm.*: Hibitane; Periochip; *Fin.*: Corsodyl; Klorhexol; Meridol Perio CHX; Periochip; Travahex; *Fr.*: Baseal; Biorgasept; Cetavlex; Collunovar; Corsodyl; Dermachrome†; Diasepryl; Dosiseptine; Elgydium; Elugel; Euraxsepti; Exoseptoplix; Hibidil; Hibiscrub; Hibisprint†; Hibitane; Paroex; Plurexid†; Prexidine; Septeal; Septidose; Septivon; Septivoncare; *Ger.*: Bactigras; Cathejell S†; Chlorhexamed; Cidegol C; Dynexan Proaktiv; Endosgel; Lemocin CX†; Meridol med CHX; *Gr.*: Hibitane; Lifo-Scrub; Periochip; Periogard; Plak Out; Spitaderm; *Hong Kong*: Bacidin†; Corsodyl; Hexidine†; Hexisol†; Hydrex; Qualikin; Scanlin; Vick-Hexidine†; *Hung.*: Septofort; *India*: A'Fresh; Afresho; Arofil; C-Nate; Clohex; CMW; Coglu; Dencure; Dentrosym; Evergaurd; Freshex; Glihex; Hexabir; Hexatrin; Hexide; Hexidine; Hexigel; Hexiprep; Hygeen; Indent; Inhex; M-Rinse; Maghex-M; Microshield; Mouden; Nitra-Hex; Nusept; O2-Fresh; Orahex; Orbiz; Orinse; Orofact; Osihex; *Indon.*: Mediscrub†; *Irl.*: Cepton Medicated; Corsodyl; Hibiscrub; Hibitane; Hydrex; Periochip; Prevora Stage 1; Savlon Antiseptic Wound Wash; Sterets Unisept; *Israel*: Bactoscrub†; Bactosept†; Cleardent; Corsodyl; GynaHex; Hexatate†; KxG; Medident; Periochip; Pharma-Dentix†; Septadine Scrub; Septal; Septalone; Septol; Tarodent; Xylodent†; *Ital.*: Benodent CLX; Broxodin; Clarifex; Clomirex†; Clorexifarm; Clorosan; Corsodyl; Dempol; Dentosan Parodontale; Eburos; Ekuba; Esoform Mani-Cute; Esosan Gel Mani; Golasan; Iodosan Clorexidina; Lenil; Master-Aid; Neo-Destomygen; Neomercurocromo; Neoxene; Neoxinal; Parodontax; Periochip; Periogard Chlorohex; Plak Out; Plak; Sicura3; Triseptil†; *Malaysia*: Baby Shield Plus; Bactigras; GynePro; Oradex; *Mex.*: Perioxidin†; *Neth.*: Corsodyl; Dettol Sterilon; Hibiscrub; Hibitane†; Hydrex†; Irrisol; Lifo-Scrub; Periochip; Urogliss-S; *Norw.*: Corsodyl; Hibiscrub; Hibitane; Periochip; *NZ*: DP Hand Rub†; Hibitane†; Riotane†; *Philipp.*: Bactigras; GynePro; Orahex; Para-Tulle; *Pol.*: Corsodyl; Septofervex†; *Port.*: Alospray; Bexident; Cloraldin†; Corsodyl; Dialens†; Handscrub; Hibitane; Lifo-Scrub†; Periochip; *Rus.*: Amident (Амидент); Elgydium (Эльгидиум); Elugel (Элюгель); Hexicon (Гексикон); *S.Afr.*: Bactigras; Corsodyl; D-Germ†; Hexidin†; Hibiscrub†; Hibitane; Orosept†; *Singapore*: Baby Shield Plus; Chlorohex; Elgydium; EluDental†; Elugel; Hexoscrub; Obstetric Care; Periochip†; Pfizer Obstetric Lotion†; Trihexid; *Spain*: Clorxil; Cristalcrom; Cristalmina; Curafil†; Cuvefilm; Deratin; Hibimax†; Hibiscrub; Menalmina; Normosept; Septisan†; *Swed.*: Corsodyl; Descutan; Hexident; Hibiscrub; Hibitane; Periochip; *Switz.*: Atoseptal; Chlorhexamed; Corsodyl; Dentohexin; DermaPlast Desinfect; Dosiseptine†; Elgydium; Hexamedal; Hibidil; Hibiscrub; Hibitane†; Lifo-Scrub; Meridol Perio; Periochip; Plak Out; *Thai.*: B-Mouthwash; Bacard Antiseptic; Bactigras; C-20; Chlorhex; Hexene; Hexide; Hexidine; Hibiscrub†; Hibitane†; Hydrex; Obitane; OR; Q-Bac†; *Turk.*: Cloder; Disinfecting†; Gargarex; Hibitanol; Klorheksol; Klorhex; Mediscrub; Oroheks; Superheks; *UAE*: Zordyl; *UK*: Acriflex; Bactigras; Cepton; Chlorohex; Corsodyl; Curasept; CX Powder; Eczmol; Elgydium; Hibiscrub; Hibitane; Hydrex; Periogard†; Savlon Antiseptic Wound Wash; Serotulle; Spotoway; Steripod Chlorhexidine Gluconate; Unisept; Uriflex C; *Ukr.*: Hexicon (Гексикон); *USA*: Betasept; Biopatch; Dyna-Hex; Exidine; Hibiclens†; Hibistat; Peridex; Periochip; Periogard; Surgilube; *Venez.*: Peridont.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Pharmacopoeial Preparations

BP 2014: Chlorhexidine Gluconate Eye Drops; Chlorhexidine Gluconate Gel; Chlorhexidine Irrigation Solution; Chlorhexidine Mouthwash; Lidocaine and Chlorhexidine Gel;
USP 36: Chlorhexidine Gluconate Oral Rinse; Chlorhexidine Gluconate Topical Solution.

Chlorinated Lime

Desmanche; Bleaching Powder; Cal clorada; Calcaria Chlorata; Calcii Hypochloris; Calcium Hypochlorite; Calcium Hypochlorosum; Calx Chlorata; Calx Chlorinata; Chloride of Lime; Chlorkalk; Chlorure de Chaux; Cloruro de Cal; Хлорная Известь.

CAS — 7778-54-3.

Pharmacopoeias. In *Br.* and *Jpn*.

BP 2014: (Chlorinated Lime). A dull white powder with a characteristic odour, containing not less than 30.0% w/w of 'available chlorine'. It becomes moist and gradually decomposes on exposure to air, carbon dioxide being absorbed and chlorine evolved. Partly soluble in water and in alcohol.

Uses and Administration

Chlorinated lime is a disinfectant and antiseptic with the general properties of chlorine (below).

Its action is rapid but brief, the 'available chlorine' soon being exhausted by combination with organic material. It is used to disinfect faeces, urine, and other organic material, and as a cleansing agent for lavatories, drains, and effluents.

Chlorinated lime is used in the preparation of Surgical Chlorinated Soda Solution (BPC 1973) (Dakin's Solution) which has been employed as a wound disinfectant, and Chlorinated Lime and Boric Acid Solution (BP 1993), (Eusol), which has been used as a disinfectant lotion and wet dressing, sometimes with equal parts of liquid paraffin. However, such solutions are irritant when applied undiluted, and are no longer recommended for use in this way. In addition, there is some evidence that such chlorine-releasing solutions may delay wound healing (see Disinfection, Wounds under Uses and Administration of Sodium Hypochlorite, p. 1769.1).

Homoeopathy

Chlorinated lime has been used in homoeopathic medicines under the following names: Calcarea hypochlorata; Calc hypochlor.

Adverse Effects, Treatment, and Precautions

As for Sodium Hypochlorite, p. 1769.2.

Preparations

Pharmacopoeial Preparations

BPC 1973: Surgical Chlorinated Soda Solution.

Chlorine

925; Chlor; Chlore; Chlorium; Cloro; Klor; Хлор.

Cl_2=70.90

CAS — 7782-50-5.
UNII — 4R7X1O2820 (chlorine); Q32ZN48698 (chloride ion).

Description. Chlorine is a greenish-yellow gas with a suffocating odour; commonly available as a pressurised liquid.

Uses and Administration

Chlorine is a disinfectant with a rapid potent brief bactericidal action. It is capable of killing most bacteria, and some fungi, yeasts, algae, viruses, and protozoa. It is slowly active against spores.

It is used for the treatment of water (p. 1731.3), but for most other purposes it is used in the form of hypochlorites, organic and inorganic chloramines, chlorinated hydantoins, chlorinated isocyanurates, and similar oxidising compounds capable of releasing chlorine. In the presence of water these compounds produce hypochlorous acid (HOCl) and hypochlorite ion (OCl^-) and it is generally considered that the lethal action on micro-organisms is due to chlorination of cell protein or enzyme systems by nonionised hypochlorous acid, although the hypochlorite ion may also contribute.

The activity of most of the compounds decreases with increase of pH, the activity of solutions of pH 4 to 7 being greater than those of higher pH values. However, stability is usually greater at an alkaline pH.

The potency of chlorine disinfectants is expressed in terms of **available chlorine**. This is based on the concept of chlorine gas (Cl_2) as the reference substance. Two atoms of chlorine (2 X Cl) yield in water only one molecule of hypochlorous acid (on which activity is based), while hypochlorites and chloramines yield one molecule of hypochlorous acid for each atom of chlorine as shown in the following equations:

$$Cl_2 + H_2O \leftrightarrow HOCl + H^+ + Cl^-$$
$$NaOCl + H_2O \leftrightarrow HOCl + NaOH$$

Thus the assayed chlorine in such compounds has to be multiplied by 2 to produce 'available chlorine'. The term 'active chlorine' has been used confusingly for either 'available chlorine' (Cl_2) or 'combined chlorine' (Cl).

Because they have relatively low residual toxicity, chlorine compounds are useful for the disinfection of relatively clean impervious surfaces, such as babies' feeding bottles, baths, and food and dairy equipment. A concentration of 100 to 300 ppm of 'available chlorine' is used; a detergent may be added to ensure wetting of the surface. Solutions containing 1000 ppm 'available chlorine' are recommended for minor surface contamination and as part of general good hygiene practice. Solutions containing 10 000 ppm 'available chlorine' are used to disinfect surfaces contaminated with spilled blood or body fluids; this strength is effective against viruses including human immunodeficiency virus (HIV) and hepatitis B virus (p. 1731.2). A concentration providing 20 000 ppm 'available chlorine' is used for material from patients with Creutzfeldt-Jakob disease (p. 1730.3).

On a large scale, chlorine gas is used to disinfect public water supplies. On a smaller scale, the use of chlorine compounds is more convenient and sodium hypochlorite, tosylchloramide sodium, chlorinated lime, chlorine dioxide, or halazone are used. After satisfying the chlorine demand (the amount of chlorine needed to react with organic matter and other substances), a free-residual content of 0.2 to 0.4 ppm 'available chlorine' should be maintained, though more is required for alkaline waters with a pH of 9 or more. For the disinfection of potentially contaminated water a concentration of 1 ppm is recommended. Excessive residual chlorine may be removed by adding a little citric acid or sodium thiosulfate.

For use in small swimming pools, sodium or calcium hypochlorite may be added daily to maintain a free-residual 'available chlorine' concentration of 1 to 3 ppm. Tosylchloramide sodium, chlorinated lime, and the isocyanurates (see Troclosene, p. 1774.1) may also be used. To minimise irritation of the eyes, maintain disinfectant activity, prevent precipitation of salts, and prevent metal corrosion, a pH of 7.2 to 7.8 should be maintained.

Solutions of chlorine-releasing compounds are also used in wound desloughing and disinfection (but see Disinfection: Wounds, under Sodium Hypochlorite, p. 1769.1).

Adverse Effects and Treatment

Chlorine gas is irritant and corrosive producing inflammation, burns, and necrosis. Inhalation may result in coughing, choking, headache, dyspnoea, dizziness, expectoration of frothy white sputum (which may be blood stained), a burning chest pain, and nausea. Bronchospasm, laryngeal oedema, acute pulmonary oedema with cyanosis, and hypoxia may occur. There may be vomiting and development of acidosis. Death may result from hypoxia.

Some of the toxicity of chlorine may be due to its dissolution in tissue water to produce hydrochloric acid and hypochlorite. After exposure to chlorine, conjunctivitis may

require a topical anaesthetic and frequent irrigations of water or saline. Respiratory distress should be treated with inhalations of humidified oxygen and bronchodilators; mechanical ventilation may be required. Corticosteroids have been given in an attempt to minimise pulmonary damage but their benefit is unproven. Acidosis may require the intravenous use of sodium bicarbonate or other suitable alkalising agent.

Effects on the eyes. Eye examinations of 50 subjects immediately before and after swimming in a chlorinated pool (chlorine range 1.0 to 1.5 ppm) showed that 68% had symptoms of corneal oedema and 94% had corneal epithelial erosions. No subject had a measurable decrease in visual acuity.[1]

1. Haag JR, Gieser RG. Effects of swimming pool water on the cornea. *JAMA* 1983; 249: 2507–8.

Effects on the respiratory tract. An assessment of 847 adolescents who attended indoor or outdoor chlorinated swimming pools, has suggested such exposure may contribute to the development of asthma, hay fever, and allergic rhinitis.[1]

1. Bernard A, *et al.* Impact of chlorinated swimming pool attendance on the respiratory health of adolescents. *Pediatrics* 2009; 124: 1110–18.

Poisoning. Experience gained from 186 cases of acute chlorine exposure indicated that medical support was required for only a short time even when exposure was repeated;[1] late sequelae were not seen, even in patients with abnormal respiratory function tests or blood gases on admission. Thirteen children who were accidentally exposed to chlorine products and gas at a community swimming pool complained of eye and throat irritation, chest pain and tightness, shortness of breath, wheezing, and anxiety and 5 children with hypoxia required hospital admission. These children received humidified oxygen, salbutamol, and, in 4 patients, methylprednisolone, and all were discharged 1 to 2 days later.[2] Another report on 76 children with chlorine poisoning revealed that the longest period of hospitalisation was 12 hours after treatment with oxygen and corticosteroids.[3] A 14-year-old boy with a history of asthma exposed to chlorine gas developed acute respiratory distress syndrome and required intubation, ventilatory support, salbutamol, and corticosteroids. He was extubated after 19 days and recovered well.[4] There have been reports of deliberate inhalation of chlorine,[5,6] in one instance for pleasure,[5] leading to severe adverse effects. Some individuals may be unduly insensitive to chlorine-induced irritation and workers should be warned that concentrations of chlorine which can be tolerated for short periods without undue discomfort can still cause serious injury which may not be immediately apparent.[6]

Guidelines[7,8] have been issued for the management of chlorine exposure.

1. Barret L, Faure J. Chlorine poisoning. *Lancet* 1984; i: 561–2.
2. Sexton JD, Pronchik DJ. Chlorine inhalation: the big picture. *Clin Toxicol* 1998; 36: 87–93.
3. Fleta J, *et al.* Intoxication of 76 children by chlorine gas. *Hum Toxicol* 1986; 5: 99–100.
4. Traub SJ, *et al.* Case report and literature review of chlorine gas toxicity. *Vet Hum Toxicol* 2002; 44: 235–9.
5. Rafferty P. Voluntary chlorine inhalation: a new form of self-abuse? *BMJ* 1980; 281: 1178–9.
6. Dewhurst F. Voluntary chlorine inhalation. *BMJ* 1981; 282: 565–6.
7. DoH. Chlorine: guidelines for action in the event of a deliberate release (issued February 2004). Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947362398 (accessed 27/08/08)
8. Agency for Toxic Substances and Disease Registry. Medical management guidelines (MMGs) for chlorine (Cl_2). Available at: http://www.atsdr.cdc.gov/MHMI/mmg172.html (accessed 15/03/06)

Precautions

The antimicrobial activity of chlorine disinfectants is reduced by the presence of organic material and by increasing pH. Hypochlorite solutions may delay wound healing (see Disinfection: Wounds under Uses and Administration of Sodium Hypochlorite, p. 1769.1).

Chlorine Dioxide

926; Cloro, dióxido de; Диоксид хлора.
ClO_2=67.45.
CAS — 10049-04-4.
UNII — 8061YMS4RM.

Profile

Chlorine dioxide is a strong oxidising agent with the general properties of chlorine (p. 1746.2). It is rapidly active against vegetative bacteria, including mycobacteria, and viruses and is also sporicidal. It is used for disinfection of medical equipment either in gaseous form or in a solution that requires activation before use and yields 700 to 1100 ppm 'available chlorine' (see p. 1746.3). Chlorine dioxide is irritant to the skin, eyes, and respiratory tract and should be stored in sealed containers. It is potentially corrosive to many materials and solutions may contain corrosion inhibitors.

Chlorine dioxide is also used for treatment and disinfection of water supplies.

General references.

1. WHO. Chlorine dioxide (gas). *Concise International Chemical Assessment Document* 37 Geneva: WHO, 2002. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad37.pdf (accessed 14/03/06)

Disinfection of endoscopes. Chlorine dioxide solutions are used as an alternative to glutaral for the disinfection of endoscopes (p. 1731.2).

Halitosis. Chlorine dioxide has been used in mouthwashes for the control of halitosis.[1]

1. Frascella J, *et al.* Odor reduction potential of a chlorine dioxide mouthrinse. *J Clin Dent* 1998; 9: 39–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Retardex; *Philipp.*: Oracare; *UK*: Retardex.

Chloroacetamide

Chloracetamide; Cloroacetamida; Хлорацетамид.
2-Chloroacetamide.
C_2H_4ClNO=93.51.
CAS — 79-07-2.
UNII — 2R97846T1L.

Profile

Chloroacetamide is a preservative that has been used in topical pharmaceutical preparations and cosmetics.

N-(3-Chloroallyl)hexaminium Chloride

N-(3-Cloroalil)hexaminio, cloruro de; Quaternium-15; Кватерниум-15.
1-(3-Chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride.
$C_9H_{16}Cl_2N_4$=251.2.
CAS — 4080-31-3.
UNII — E40U03LEM0; 2W5B4VJ152 (trans-form).

Profile

N-(3-Chloroallyl)hexaminium chloride is an antimicrobial preservative used in pharmaceutical preparations and cosmetics. Skin reactions have been reported.

Chlorobutanol *(BAN, rINN)*

Acetone-Chloroforme; Alcohol Trichlorisobutylicus; Chlorbutanol; Chlorbutanolum; Chlorbutol; Chloretone; Chlorobutanolis; Chlorobutanolum; Clorobutanol; Klooributanoli; Klorbutanol; Klorobutanol; Trichlorbutanolum; Хлоробутанол.
1,1,1-Trichloro-2-methylpropan-2-ol.
$C_4H_7Cl_3O$=177.4.
CAS — 57-15-8 (anhydrous chlorobutanol); 6001-64-5 (chlorobutanol hemihydrate).
ATC — A04AD04.
ATC Vet — QA04AD04.
UNII — HM4YQM8WRC (chlorobutanol); 3X4P6271OX (chlorobutanol hemihydrate).

Pharmacopoeias. *Eur.* (see p. vii), *Int.*, and *USNF* allow either the anhydrous form or the hemihydrate; *Eur.* includes them as separate monographs. *Chin.* specifies the hemihydrate. *Jpn* permits up to 6% of water.

Ph. Eur. 8: (Chlorobutanol Hemihydrate; Chlorobutanol BP 2014). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 78 degrees. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

Ph. Eur. 8: (Chlorobutanol, Anhydrous). A white or almost white, crystalline powder or colourless crystals. It sublimes readily. M.p. about 95 degrees. Slightly soluble in water; very soluble in alcohol; soluble in glycerol (85%). Store in airtight containers.

USNF 31: (Chlorobutanol). It is anhydrous or contains not more than one-half molecule of water of hydration. Colourless or white crystals with a characteristic, somewhat camphoraceous odour. M.p. about 76 degrees for the hemihydrate and about 95 degrees for the anhydrous form. Soluble 1 in 125 of water, 1 in 1 of alcohol, and 1 in 10 of glycerol; freely soluble in chloroform, in ether, and in volatile oils. Store in airtight containers.

Incompatibility and stability. The activity of chlorobutanol can be adversely affected by the presence of other compounds as well as by the packaging material. There may be sorption onto substances like magnesium trisilicate, bentonite, carmellose,[1] polyethylene,[2,3] or polyhydroxyethylmethacrylate that has been used in soft contact lenses.[4] Increasing heat[2,3] or pH[5,6] can reduce stability and activity.

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; 8: 54–6.
2. Priesen WT, Plein EM. The antibacterial stability of chlorobutanol stored in polyethylene bottles. *Am J Hosp Pharm* 1971; 28: 507–12.
3. Holdsworth DG, *et al.* Fate of chlorbutol during storage in polyethylene dropper containers and simulated patient use. *J Clin Hosp Pharm* 1984; 9: 29–39.
4. Richardson NB, *et al.* The interaction of preservatives with polyhydroxyethylmethacrylate (polyHEMA). *J Pharm Pharmacol* 1978; 30: 469–75.
5. Nair AD, Lach JL. The kinetics of degradation of chlorobutanol. *J Am Pharm Assoc (Sci)* 1959; 48: 390–5.
6. Patwa NV, Huyck CL. Stability of chlorobutanol. *J Am Pharm Assoc* 1966; NS6: 372–3.

Uses and Administration

Chlorobutanol has antibacterial and antifungal properties and it is used at a concentration of 0.5% as a preservative in injections and in eye drops as well as cosmetics.

Chlorobutanol has been used as a mild sedative and local analgesic but other compounds are preferred. It has been used in preparations for inflammatory and painful conditions of the ear and oropharynx.

Adverse Effects

Acute poisoning with chlorobutanol may produce CNS depression with weakness, loss of consciousness, and depressed respiration. Delayed (type IV) hypersensitivity reactions have been reported rarely.

References.

1. Nordt SP. Chlorobutanol toxicity. *Ann Pharmacother* 1996; 30: 1179–80.

Effects on the cardiovascular system. Rapid falls in arterial blood pressure were noted after injections of heparin containing chlorobutanol in patients undergoing coronary bypass.[1] No fall in blood pressure was seen in patients who received preservative-free heparin injection.

1. Bowler GMR, *et al.* Sharp fall in blood pressure after injection of heparin containing chlorbutol. *Lancet* 1986; i: 848–9.

Effects on mental function. The sedative effects of chlorobutanol have been reported to be a problem in a patient dependent on large doses (0.9 to 1.5 g daily with salicylamide 1.8 to 3.0 g daily)[1] and in another patient given high doses of morphine in an infusion preserved with chlorobutanol.[2]

1. Borody T, *et al.* Chlorbutol toxicity and dependence. *Med J Aust* 1979; i: 288.
2. DeChristoforo R, *et al.* High-dose morphine infusion complicated by chlorobutanol-induced somnolence. *Ann Intern Med* 1983; 98: 335–6.

Hypersensitivity. A delayed, cellular type of hypersensitivity reaction to chlorobutanol used to preserve heparin injection after subcutaneous injection has been reported.[1] Pruritus from intranasal desmopressin has been attributed to the chlorobutanol preservative.[2]

1. Dux S, *et al.* Hypersensitivity reaction to chlorbutanol-preserved heparin. *Lancet* 1981; i: 149.
2. Itabashi A, *et al.* Hypersensitivity to chlorobutanol in DDAVP solution. *Lancet* 1982; i: 108.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Cerax; Eludril; Otocalmia; *Austral.*: Cerumol; *Belg.*: Eludril; Givalex; Prurisedine†; *Braz.*: Auritricin; *Canad.*: Cerumol; DSO Dressing; Larynsol†; Neutralite; *Chile*: Eludril; *Fr.*: Alodont; Angispray; Balsamorhinol; Buccosoin; Eludril; Eludrilpro; Givalex; *Gr.*: Evex; Heludril; *India*: Andre; Borozin; Ceruklin; Clearwax; Desol; Despol; Dewax; Fastwax; I-Top; Moss Eye; Nayawax; Nill-O-Wax; Otoclean; Otorex; Parabec; Waxolve†; *Irl.*: Cerumol; Eludril†; Karvol; *Israel*: Cepadont†; Cerumol; Dentin; Karvol; Pitrisan†; *Ital.*: Fialetta Odontalgica Dr Knapp; Gocce Odontalgiche; *Malaysia*: Cerumol; *NZ*: Fradon†; *Port.*: Eludril; Otoceril; *Rus.*: Cameton (Каметон); Eludril (Элюдрил); *S.Afr.*: Aurone Forte†; Cerumol; Chamberlains Traditional Colic Remedy†; Karvol†; *Singapore*: Cerumol; Eludril; Karvol; *Spain*: Eludril†; Otocerum; *Switz.*: Baume Dalet; Cerumenol; Eludril; *Thai.*: Opplin; Optal; Optic; *Turk.*: Disinol; *UK*: Cerumol; Cetanorm; DDD; DDD; Dermidex; Eludril; Fradon; Karvol; *Ukr.*: Angilex (Ангилекс); Givalex (Гивалекс); Heppylor (Хепилор); *USA*: Outgro.

Chlorocarvacrol

5-Chlorocarvacrol; Clorcarvacrol; Clorcarvacrolum; Kloorikarvakroli; Klorkarvakrol; Monochloroisothymol.
4-Chloro-5-isopropyl-2-methylphenol.

$C_{10}H_{13}ClO$=184.7
CAS — 5665-94-1.

Profile

Chlorocarvacrol is a phenolic antiseptic that is used as an ingredient of preparations for anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Delta-Hadensa; Hadensa; Hadensa; Haemanal; *Chile*: Vatanal; *Fin.*: Hadensa†; Hadensa; *Neth.*: Epianal; *Norw.*: Alcos-Anal; *Spain*: Hadensa; *Turk.*: Hedensa.

Chlorocresol *(USAN, rINN)*

Chlorkresol; Chlorkresolum; Chlorocrésol; Chlorocresolum; Chlorokrezolis; Clorocresol; Kloorikresoli; Klorkresol; Klorokrezol; Parachlorometacresol; PCMC; Хлорокрезол.
p-Chloro-*m*-cresol; 4-Chloro-3-methylphenol.
C_7H_7ClO=142.6
CAS — 59-50-7.
UNII — 36W53O7109.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Chlorocresol). A white or almost white, crystalline powder or compacted crystalline masses supplied as pellets or colourless or white crystals. M.p. 64 degrees to 67 degrees. Slightly soluble in water; very soluble in alcohol; freely soluble in fatty oils. It dissolves in solutions of alkali hydroxides. Protect from light.

USNF 31: (Chlorocresol). Colourless or practically colourless crystals or crystalline powder with a characteristic nontarry odour; it is volatile in steam. M.p. 63 degrees to 66 degrees. Soluble 1 in 260 of water; more soluble in hot water; soluble 1 in 0.4 of alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. Chlorocresol has long been recognised to be incompatible with a range of compounds including: calcium chloride, codeine phosphate, diamorphine hydrochloride, papaveretum, quinine hydrochloride,[1] methylcellulose,[2] and nonionic surfactants[3,4] such as cetomacrogol 1000 and polysorbate 80.

1. McEwan JS, Macmorran GH. The compatibility of some bactericides. *Pharm J* 1947; 158: 260–2.
2. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; 42: 583–8.
3. *PSGB Lab Report* P/70/15 1970.
4. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; 8: 54–6.

Uses and Administration

Chlorocresol is a potent chlorinated phenolic disinfectant and antiseptic. It has bactericidal activity against Gram-positive and Gram-negative bacteria and is effective against fungi but has little activity against bacterial spores except at high temperatures. It is more active in acid than in alkaline solution.

Chlorocresol is used in preparations for disinfection of the skin and wounds. It is also used as a preservative in cosmetics and in creams and other preparations for external use that contain water.

Chlorocresol is used as a preservative in aqueous injections issued in multidose containers. It may also be added to aqueous preparations that cannot be sterilised in their final containers and have to be prepared using aseptic precautions. Concentrations of 0.1% have generally been used. Injections prepared with chlorocresol should not be injected into the CSF, the eye, or the heart. Also such injections should generally not be given in volumes greater than 15 mL. Sterilisation by heating with a bactericide such as chlorocresol is no longer a recommended practice.

Adverse Effects, Treatment, and Precautions

As for Phenol, p. 1764.2. The antimicrobial activity of chlorocresol may be reduced by incompatibility (see above), adsorption, increasing pH, or through combination with organic matter (including oils and fats) or nonionic surfactants.

Chlorocresol is less toxic than phenol. Sensitisation reactions may follow application to the skin and hypersensitivity has occurred after systemic use of injections containing chlorocresol as a preservative.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Perfungol†; Perfungol; *Cz.*: Cyteal; *Fr.*: Cicatryl; Cyteal; *Ger.*: Bomix†; Helipur; *Gr.*: Lyoderm; Octrene; *Hong Kong*: Acnesol†; *India*: Balderm; Bedex-GM; *Irl.*: Anbesol; Cymex; *Ital.*: Helipur; Hygienist; *Philipp.*: Cyteal; *Port.*: Cyteal; *Rus.*: Cyteal (Цитеал); *S.Afr.*: Anbesol†; *Singapore*: Cyteal; *UK*: Anbesol; Cymex; Cyteal; Valderma; *Ukr.*: Cyteal (Цитеал).

Pharmacopoeial Preparations
BPC 1973: Proflavine Cream.

Chlorothymol

Clorotimol; Monochlorothymol; Хлоротимол.
6-Chlorothymol; 4-Chloro-2-isopropyl-5-methylphenol.
$C_{10}H_{13}ClO$=184.7
CAS — 89-68-9.
UNII — U25TI0CVT.

Profile

Chlorothymol is a chlorinated phenolic antiseptic used as an ingredient of preparations for hand and skin disinfection and topical treatment of fungal infections. It has also been used in preparations for anorectal disorders, cold symptoms, and mouth disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Pioral Pasta.

Multi-ingredient Preparations. *India*: Aerway; Coriminic-Vaporise; Easi Breathe; Genvol Plus; Karvol Plus; Kolq Inhalant; Sinarest Vapocaps; *Ital.*: Labocaina; Vagisil; *Philipp.*: Calmoseptine.

Chloroxylenol *(BAN, USAN, rINN)*

Chloroxylénol; Chloroxylenolum; Cloroxilenol; Parachlorometaxylenol; PCMX; Хлорксиленол.
4-Chloro-3,5-xylenol; 4-Chloro-3,5-dimethylphenol.
C_8H_9ClO=156.6
CAS — 88-04-0.
ATC — D08AE05.
ATC Vet — QD08AE05.
UNII — 0F32U78V2Q.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Chloroxylenol). White or cream crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol; soluble in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

USP 36: (Chloroxylenol). White crystals or crystalline powder with a characteristic odour; volatile in steam. Very slightly soluble in water; freely soluble in alcohol, in ether, in terpenes, in fixed oils, and in solutions of alkali hydroxides.

Incompatibility. Chloroxylenol has been reported to be incompatible with nonionic surfactants and methylcellulose.

Uses and Administration

Chloroxylenol is a chlorinated phenolic antiseptic that is bactericidal against most Gram-positive bacteria but less active against staphylococci and Gram-negative bacteria, and is often inactive against *Pseudomonas* spp. Its activity against *Ps. aeruginosa* appears to be increased by the addition of edetic acid. It is inactive against bacterial spores.

Chloroxylenol Solution (BP 2014) is used for skin and wound disinfection, and chloroxylenol is used as a preservative in a variety of other topical formulations.

Adverse Effects and Precautions

Chloroxylenol in the recommended dilutions is generally non-irritant but skin sensitivity has occurred. There have been isolated reports of poisoning. Symptoms reported include corrosion of the oral mucosa, larynx, and the gastrointestinal tract, bradycardia, hypotension, and renal failure. Large amounts may cause CNS depression. Pulmonary aspiration of chloroxylenol-based disinfectants may result in pneumonia, acute respiratory distress syndrome, and cardiorespiratory arrest.

The antimicrobial activity of chloroxylenol may be diminished through combination with organic matter. Aqueous solutions of chloroxylenol may be susceptible to contamination with micro-organisms. To reduce this risk, solutions must be freshly prepared at the recommended concentration and appropriate measures should be taken to prevent contamination during storage or dilution.

Poisoning. Reports of fatal or severe self-poisoning with chloroxylenol solution.[1-5]

1. Meek D, *et al.* Fatal self-poisoning with Dettol. *Postgrad Med J* 1977; 53: 229–31.
2. Joubert P, *et al.* Severe Dettol (chloroxylenol and terpineol) poisoning. *BMJ* 1978; 1: 890.
3. Chan TYK, *et al.* Chemical gastro-oesophagitis, upper gastrointestinal haemorrhage and gastroscopic findings following Dettol poisoning. *Hum Exp Toxicol* 1995; 14: 18–19.
4. Chan TY, Critchley JA. Pulmonary aspiration following Dettol poisoning: the scope for prevention. *Hum Exp Toxicol* 1996; 15: 843–6.
5. Joynt GM, *et al.* Delayed upper airway obstruction: a life-threatening complication of Dettol poisoning. *Anaesthesia* 1997; 52: 261–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Espadol; Talowin; *Austral.*: Dettol; *Belg.*: Dettol; *Canad.*: Antibacterial; Colourless Antiseptic Contact; Dermex I; Dettol; Digiclean E Foam Hand Soap; Epi Wash†; Epicare; Germicidal Hand Soap; Grasp; Health Care Antiseptic Soap; Health Care E-2 Antis Lot Soap; Kimcare Antibacterial†; Medi-Scrub; Micrell; Phenrex; Prime Source with Chloroxylenol; Provon Antimicrobial; Provon Medicated with Chloroxylenol; Septiline; Soft Care Antiseptic; Soft Care Sanitizing; Softcide Handwash; Surgical Scrub and Handwash; Virobex-P; *Cz.*: Dettolmed; *Gr.*: Dettol; Dettolsept; *Hong Kong*: Dettol†; New Dettol†; *Irl.*: Dettol; *Ital.*: Neomercurocromo; *Malaysia*: Dettol; *Neth.*: Dettol; *NZ*: Dettol; *S.Afr.*: Dettol; *Singapore*: Dettol; *Thai.*: Dettol; *UK*: Dettol.

Multi-ingredient Preparations. *Arg.*: Jabonacid; Kytinon ATM; Previnfec; ZeaSorb; *Austral.*: Dettol Cream; ZeaSorb†; *Canad.*: Antiseptic Lotion†; Ensuite; Inhibit; Sani-Dex†; Soothing Foot Spray; Uphold Plus; ZeaSorb; *Chile*: Dermac Crema; *Hong Kong*: Acne-Aid†; Dettol†; *India*: Dettol Obstetric; Dettol; Dettolin; *Indon.*: ZeaSorb; *Irl.*: Dettol†; Rinstead; TCP; ZeaSorb; *Israel*: Gargol; Hemo; Rexitol†; *Ital.*: Foille Scottature; Foille Sole; *Malaysia*: Acne-Aid†; Dettol; *NZ*: Dettol; *Philipp.*: Strepsils; ZeaSorb; *Pol.*: Sterovag†; *S.Afr.*: Respisniffers†; Woodwards Inhalant; ZeaSorb†; *Singapore*: Acne-Aid†; Dettol; ZeaSorb; *Thai.*: Dettol; ZeaSorb†; *UK*: Dettol; Eradicil; Rinstead; Skintex; TCP; ZeaSorb; *USA*: Calamycin; Cortamox†; Cortane-B; Cortic ND; Cyotic; Dermacoat; Foille; Fungi-Nail; Geri-Lav Free; Gordochom; Lobana Peri-Garde; Mediotic-HC; Oticin HC; Oticin; Oto-End; Otomar-HC; PramOtic; TriOxin; Unguentine Plus; Zinotic†; Zoto-HC.

Pharmacopoeial Preparations
BP 2014: Chloroxylenol Solution.

Cicliomenol *(rINN)*

Cicliménol; Ciclomenolum; Циклиомéнол.
2-Cyclohexyl-4-iodo-3,5-xylenol.
$C_{14}H_{19}IO$=330.2
CAS — 10572-34-6.
UNII — GYU56H6EBV.

Profile

Cicliomenol is an antiseptic included in preparations intended for the topical treatment of mouth and throat infections.

Cinnamic Acid

Cinámico, ácido; Cinnamylic Acid; Коричная Кислота.
trans-3-Phenylpropenoic acid.
$C_6H_5.CH:CH.CO_2H$=148.2
CAS — 621-82-9.
UNII — U14A832J8D.

Pharmacopoeias. In *Br.*

BP 2014: (Cinnamic Acid). Colourless crystals with a faint balsamic odour. Very slightly soluble in water; freely soluble in alcohol; soluble in chloroform and in ether.

Profile

Cinnamic acid has preservative properties. It is used with benzoic acid and other substances to simulate the flavour of tolu.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Novobroncol; *Irl.*: Hemocane; *UK*: Hemocane; Potters Gees Linctus; Sanderson's Throat Specific.

Pharmacopoeial Preparations
BP 2014: Tolu-flavour Solution.

Clorophene *(USAN)*

Clorfene; Clorofene (pINN); Clorofène; Clorofeno; Clorofenum; NSC-59989; Septiphene; Хлорофен.
2-Benzyl-4-chlorophenol.
$C_{13}H_{11}ClO$=218.7.
CAS — 120-32-1.
UNII — 7560BB0B03.

Profile

Clorophene is a chlorinated phenolic antiseptic stated to be active against a wide range of bacteria, fungi, protozoa, and viruses. It is used as a skin disinfectant and for surface and instrument disinfection. Clorophene sodium has also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Neo-Sabenyl; *Canad.*: Aseptone 1; Aseptone 2; Aseptone 5; *Ger.*: Bomix†; Preka-Derm†; Freka-Sept 80†; Helipur; *Ital.*: Helipur; Hygienist; *UAE*: Radol; *USA*: BTK-Plus†.

Cresol

Crésol brut (cresol, crude); Cresolum; Cresolum crudum (cresol, crude); Cresylic Acid; Kresol; Kresol, rå (cresol, crude); Kresoli, raaka (cresol, crude); Kresolum Venale; Krezol; Krezolis, negrynintas (cresol, crude); Metacresol (BAN); Metilfenol; Tricresol; Trikresolum; Крезол.

Methylphenol.

C_7H_8O=108.1

CAS — 1319-77-3; 95-48-7 (o-cresol); 108-39-4 (m-cresol); 106-44-5 (p-cresol).

UNII — GF3CGH8D7Z (cresol); GGO4Y809LO (m-cresol); YW84DH5I7U (o-cresol); 1MXY2UM8NV (p-cresol).

NOTE. Some grades of mixed cresols may be equivalent to Tar Acids (p. 1771.2).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF*.

Eur. also includes metacresol.

Ph. Eur. 8: (Cresol, Crude; Cresolum Crudum). A mixture of *o*-, *m*-, and *p*-methylphenol. A colourless or pale brown liquid. Relative density 1.029 to 1.044. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Protect from light.

Ph. Eur. 8: (Metacresol; Metacresolum). A colourless or yellowish liquid. Relative density about 1.03. M.p. about 11 degrees. Sparingly soluble in water; miscible with alcohol and with dichloromethane. Store in airtight containers. Protect from light.

USNF 31: (Cresol). A mixture of cresol isomers obtained from coal tar or petroleum. A colourless, yellowish to brownish-yellow, or pinkish, highly refractive liquid, becoming darker with age or on exposure to light, with a phenol-like, sometimes empyreumatic odour. Specific gravity 1.030 to 1.038. Sparingly soluble in water, usually forming a cloudy solution; miscible with alcohol, with ether, and with glycerol; dissolves in solutions of fixed alkali hydroxides. A saturated solution in water is neutral or slightly acid to litmus. Store in airtight containers. Protect from light.

Profile

Cresol is a disinfectant with a similar action to phenol (p. 1763.3); suitable precautions should be taken to prevent absorption through the skin.

It has been used as Cresol and Soap Solution (BP 1968) (Lysol) as a general disinfectant but it has been largely superseded by other, less irritant, phenolic disinfectants. Cresol has been used in dentistry, alone or with formaldehyde, but is caustic to the skin and unsuitable for skin and wound disinfection. The cresols have been widely used in disinfectants for domestic and hospital use. Cresol is also used as an antimicrobial preservative in parenteral pharmaceutical preparations and in some topical formulations.

Poisoning. References to poisoning with cresol solutions.[1-7]

1. Côté M-A, *et al.* Acute Heinz-body anaemia due to severe cresol poisoning: successful treatment with erythrocytapheresis. *Can Med Assoc J* 1984; **130**: 1319–22.
2. Wu ML, *et al.* Concentrated cresol intoxication. *Vet Hum Toxicol* 1998; **40**: 341–3.
3. Hashimoto T, *et al.* Marked increases of aminotransferase levels after cresol ingestion. *Am J Emerg Med* 1998; **16**: 667–8.
4. Sakai Y, *et al.* Chemical burn with systemic cresol intoxication. *Pediatr Int* 1999; **41**: 174–6.
5. Monma-Ohtaki J, *et al.* An autopsy case of poisoning by massive absorption of cresol a short time before death. *Forensic Sci Int* 2002; **126**: 77–81.
6. Hayakawa M. Severe hepatic dysfunction following cresol poisoning. *Intensive Care Med* 2002; **28**: 1190–1.
7. Kamijo Y, *et al.* Hepatocellular injury with hyperaminotransferasemia after cresol ingestion. *Arch Pathol Lab Med* 2003; **127**: 364–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Creolina.

Multi-ingredient Preparations. *Arg.*: Algiodent; Sulfanoral T; *Austral.*: Formo-Cresol Mitis†; *Fr.*: Cidapex†; Endotine; Mepacyl; *Switz.*: Eau Precieuse; *USA*: Cresylate.

Dapabutan *(rINN)*

Dapabutano; Dapabutanum; Dodecylaminopropyl-β-aminobutyric acid; Дапабутан.

(±)-3-[[3-(Dodecylamino)propyl]amino]butyric acid.

$C_{19}H_{40}N_2O_2$=328.5

CAS — 6582-31-6.

UNII — 1R0Y7O07NF.

Profile

Dapabutan is a beta aminobutyric acid derivative used as an antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Sterlane.

Decamethoxine

Dekametoksin; Декаметоксин.

N,N,N′,N′-Tetramethyl-*N,N′*-bis(2-[[5-methyl-2-(1-methylethyl)-cyclohexyl]oxy]-2-oxoethyl)-1,10-decanediaminium dichloride.

$C_{38}H_{74}Cl_2N_2O_4$=693.9

CAS — 38146-42-8.

Profile

Decamethoxine is a quaternary ammonium antiseptic and disinfectant with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used topically for disinfection of the skin and mucous membranes and for disinfection of equipment. Decamethoxine is also used as a gargle for infections of the oral cavity and has been used topically or as an irrigation for infections of the skin and various body cavities.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Oftadek (Офтадек); *Ukr.*: Decasan (Декасан); Horosten (Горостен).

Dehydroacetic Acid

Deshidroacético, ácido; Methylacetopyronone; Дегидроацетовая Кислота.

3-Acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione (keto form); 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (enol form).

$C_8H_8O_4$=168.1

CAS — 520-45-6 (keto form); 771-03-9 (enol form).

UNII — 2KAG279R6R.

Pharmacopoeias. In *USNF*.

USNF 31: (Dehydroacetic Acid). A white or nearly white, crystalline powder. Very slightly soluble in water; soluble in aqueous solutions of alkalis. One g dissolves in about 35 mL of alcohol and in 5 mL of acetone.

Sodium Dehydroacetate

Dehydracetic Sodium; Deshidroacetato sódico; Дегидроацетат Натрия.

The sodium salt of 3-acetyl-6-methyl-2*H*-pyran-2,4(3*H*)-dione.

$C_8H_7NaO_4$=190.1

CAS — 4418-26-2.

UNII — 8W46YN971G.

Pharmacopoeias. In *USNF*.

USNF 31: (Sodium Dehydroacetate). A white or practically white, odourless powder. Freely soluble in water, in glycerol, and in propylene glycol.

Incompatibility. The activity of sodium dehydroacetate may be reduced by alkaline pH or interaction with nonionic surfactants.

Profile

Dehydroacetic acid and sodium dehydroacetate have some antifungal activity and have been used in the preservation of cosmetics and oral preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Venez.*: Photoderm AKN.

Dequalinium Chloride *(BAN, rINN)*

BAQD-10; Cloruro de decualinio; Cloruro de dequalinio; Decalinium Chloride; Decaminium; Decualinio, cloruro de; Dekalinyum Klorür; Dekvalinio chloridas; Dekvalinium dichloridi; Dekvaliniumklorid; Dekvalinium-klorid; Dekvaliniumkloridi; Dequalinii chloridum; Dequalinii Dichloridum; Déqualinium, Chlorure de; Dequaliniumchlorid; Декваминия Хлорид.

N,N-Decamethylenebis(4-amino-2-methylquinolinium chloride).

$C_{30}H_{40}Cl_2N_4$=527.6

CAS — 6707-58-0 (dequalinium); 522-51-0 (dequalinium chloride); 4028-98-2 (dequalinium acetate); 16022-70-1 (dequalinium salicylate).

ATC — D08AH01; G01AC05; R02AA02.

ATC Vet — QD08AH01; QG01AC05; QR02AA02.

UNII — XYS8INN1I6.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dequalinium Chloride). A white or yellowish-white, hygroscopic powder. Slightly soluble in water and in alcohol. Store in airtight containers.

Incompatibility. Dequalinium chloride is incompatible with soaps and other anionic surfactants, with phenol, and with chlorocresol.

Profile

Dequalinium chloride is a bisquaternary quinolinium antiseptic, bactericidal against many Gram-positive and Gram-negative bacteria, and effective against fungi. It is mainly used in the form of lozenges in the treatment of minor infections of the mouth and throat. It has been applied topically in the treatment of skin and vaginal infections.

Dequalinium salicylate and undecenoate have also been used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austria*: Evazol; Tonsillol; *Belg.*: Anginol; Laryngarsol†; *Canad.*: Dequadin; *China*: Delin (利林); Qingli (清利); *Cz.*: Naxyl; *Ger.*: Evazol†; Fluomizin; Fluomycin N†; Gurgellosung-ratiopharm; Sorot†; *Gr.*: Decosan; *Hong Kong*: Christon†; Decol†; Delin; Dequadin; Dexxon; Fluomizin; Nofrozic†; Roxine†; *India*: Dequadin; *Indon.*: Decamedin; Degirol; SP Troches; *Irl.*: Dequadin; *Ital.*: Dequadin; Dequosangola; Faringina; Goladin; Osangin; Pumilsan; *Malaysia*: Delin; Dequadin; DQM; Roxine; SP Troches; *Neth.*: Natterman Streptofree; *Philipp.*: Dequadin; *Rus.*: Fluomisin (Флуомизин); *Singapore*: Beacons DQ; Dequa-loz; Dequadin; SP Troches; *Switz.*: Decatylene†; Fluomizin; *Thai.*: Baron; Dechot; Deot; Dequadin†; Fluomizin; V Day Lozenges; *Turk.*: Dequadin; Donaxyl; *UK*: Dequadin; Labosept; *Ukr.*: Fluomizin (Флуомизин); *Venez.*: Dequadin; Laimolin.

Multi-ingredient Preparations. *Austria*: Dequalinetten; Dequonal; Eucillin; Fluorex Plus; *Belg.*: Angin-San; Anginol-Lidocaine; Dequalid; Ororhinathiol; *Braz.*: Dequadin; *China*: Deq (得益); *Ger.*: Dequonal; Ephepect-Blocker-Pastillen N; Jasimenth CN; Wick Sulagil; *Hong Kong*: Decatylen; Deq; Ephepect Blocker; Liqualon†; Quadezyme; Scassh Trouch Lozenge; *Indon.*: Sentril†; *Irl.*: Dequacaine; *Ital.*: Lisomucil Gola; Transpulmina Gola; *Malaysia*: Decatylen; Deq; Upha Lozenges; *Mex.*: Angenovag; *Norw.*: Apolar med dekvalin; *Pol.*: Tetesept†; *Port.*: Anginova; Decatyleno; Dek; Medifon†; *S.Afr.*: Dequadin Mouth Paint; *Singapore*: Decatylen; Deq; *Spain*: Anginovag; Roberfarin; *Switz.*: Anginova; Arbid-top; Decasept N†; Decatylene Neo; Dequonal; Tyroqualine; *Thai.*: Deq; Sentril†; *UK*: Dequacaine; *Ukr.*: Anginovag (Ангиноваг); Decatylen (Декатилен); Efisol (Эфизол); Lisak (Лизак); Lizak (Лизак); *Venez.*: Alantamida; Benzodiazol; Laimoqualin.

Diacetylaminoazotoluene

Diacetazotol; Diacetilaminoazotoluene; Pellidol; Диацетиламиноазотолуол.

4-Diacetylamino-2′,3-dimethylazobenzene.

$C_{18}H_{19}N_3O_2$=309.4

CAS — 83-63-6.

Profile

Diacetylaminoazotoluene is an antiseptic that has been used topically to promote wound healing.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Dermowund†.

Diazolidinyl Urea

Diazolidinylurea.
N-[1,3-Bis(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-*N,N'*-bis(hydroxymethyl)urea.
$C_8H_{14}N_4O_7$=278.2
CAS — 78491-02-8.
UNII — H5RIZ3MPW4.

Profile

Diazolidinyl urea is an imidazolidinyl preservative with similar properties and uses to imidurea (p. 1758.2).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Eucerin Piel Grasa†; *India*: Emolene.

Dibrompropamidine Isetionate *(BANM, rINNM)*

Dibromipropamidlinidi-isetionaatti; Dibromopropamidine Isethionate; Dibromopropamidyny diizetionian; Dibrompropamidina, isetionato de; Dibrompropamidindiisetionat; Dibrompropamidin-diisetionát; Dibrompropamidine Diisetionate; Dibrompropamidine, diisétionate de; Dibrompropamidine, Isétionate de; Dibrompropamidini Diisetionas; Dibrompropamidini Isetionas; Isetionato de dibrompropamidina; Дибромпропамидина Изетионат.
3,3'-Dibromo-4,4'-trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).
$C_{17}H_{18}Br_2N_4O_2.2C_2H_6O_4S$=722.4
CAS — 496-00-4 (dibrompropamidine); 614-87-9 (dibrompropamidine isetionate).
ATC — D08AC01; S01AX14.
ATC Vet — QD08AC01; QS01AX14.
UNII — 12Y597MO62.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Dibrompropamidine Diisetionate). A white or almost white, crystalline powder. Freely soluble or soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. A 5% solution in water has a pH of 5.0 to 6.0.

Profile

Dibrompropamidine isetionate is an aromatic diamidine antiseptic similar to propamidine (p. 1767.3). It is bactericidal against Gram-positive bacteria but is less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties. It is available as topical preparations for the local treatment of minor eye and skin infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Brulidine†; *Irl.*: Brolene; Golden Eye; *Norw.*: Brulidine; *NZ*: Brolene; *S.Afr.*: Brolene; *UK*: Brolene; Brulidine; Golden Eye Ointment; Pickles Antiseptic Cream.

Multi-ingredient Preparations. *UK*: Healthy Feet; No-Sor Nose Balm; RBC; Swarm.

Dichlordimethylhydantoin

Diclorodimetilhidantoína.
1,3-Dichloro-5,5-dimethylhydantoin; 1,3-Dichloro-5,5-dimethylimidazolidine-2,4-dione.
$C_5H_6Cl_2N_2O_2$=197.0
CAS — 118-52-5.

Profile

Dichlordimethylhydantoin is a disinfectant used as a source of chlorine, for sterilising food and dairy equipment and as a bleach. It contains about 72% w/w of 'available chlorine' (see p. 1746.3).

Bromochlorodimethylhydantoin ($C_5H_6N_2O_2BrCl$ = 241.5) is a closely related bromine-releasing compound used for the disinfection of swimming-pool water.

Dichlorobenzyl Alcohol

Alcohol diclorobencílico; 2,4-Dichlorbenzyl-alcoholum; Dichlorophenylcarbinol; 2,4-Diklooribentsyyli-alkoholi; 2,4-Diklorbensylalkohol; Diklorobenzil Alkol; Дихлорбензиловый Спирт.
2,4-Dichlorobenzyl alcohol.
$C_7H_6Cl_2O$=177.0
CAS — 1777-82-8.
ATC — R02AA03.
ATC Vet — QR02AA03.
UNII — 1NKX3648J9.

Profile

Dichlorobenzyl alcohol is an antiseptic used chiefly as an ingredient of lozenges in the treatment of minor infections of the mouth and throat.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies dichlorobenzyl alcohol as possibly porphyrinogenic; it should be used only when no safer alternative is available and precautions should be considered in vulnerable patients.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Neo Borocillina Collutorio; Neo Borocillina Spray.

Multi-ingredient Preparations. *Arg.*: Strepsils Plus; Strepsils; *Austral.*: Ayrtons Antiseptic; Logicin Rapid Relief; Strepsils Numbing; Strepsils Plus†; Strepsils; *Austria*: Coldangin; Neo-Angin; Sulgan 99; *Belg.*: Strepsils + Lidocaine; Strepsils Cool Mint; Strepsils Menthol†; Strepsils Vit C; Strepsils; *Canad.*: Cepacol Sensations Cooling; Cepacol Sensations Sore Throat & Blocked Nose; Cepacol Sensations Sore Throat & Cough; Cepacol Sensations Warming; Cepacol Sensations; Strepsils Cherry†; Strepsils Cool; Strepsils Sore Throat Blocked Nose; Strepsils; *Chile*: Hansaplast Antimicotico†; *Cz.*: Neo-Angin; Strepsils Cooling Mint; Strepsils Menthol a Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; *Denm.*: Strepsils; *Fin.*: Bafucin; Med-Angin; Strepsils Menthol; Strepsils; *Fr.*: Strepsils Lidocaine; Strepsils Miel-Citron; Strepsils Vitamine C; Strepsils; Strepsilspray; *Ger.*: Dobendan Cool†; Dobendan Junior; Dobendan Synergie; Dobendan Warm; Neo-Angin; *Gr.*: Strepsils Plus; Strepsils; *Hong Kong*: Logicin Rapid Relief; Strepsils Dual Action; Strepsils; *Hung.*: Neo-Angin; Strepsils Menthol and Eucalyptus; Strepsils Plus; Strepsils Vitamin C; Strepsils; *India*: Cofsils; *Irl.*: Strepsils +Plus Anaesthetic; Strepsils Cool; Strepsils Dual Action†; Strepsils Sore Throat and Blocked Nose; Strepsils Throat; Strepsils Vitamin C; Strepsils; *Israel*: Strepsils Plus; Strepsils with Menthol and Eucalyptus; Strepsils with Vitamin C; Strepsils; *Ital.*: Arscolloid; Benagol Mentolo-Eucaliptolo; Benagol Vitamina C; Benagol; Bioarscolloid; Corti-Arscolloid; Neo Borocillina Balsamica; Neo Borocillina C; Neo Borocillina Tosse Compresse; Neo Borocillina; *Malaysia*: Chericof; Strepsils Dual Action; Strepsils; *Neth.*: Strepsils Menthol & Eucalyptus†; Strepsils Sinaasappel & Vitamine C; Strepsils; *NZ*: Strepsils Plus Anaesthetic; Strepsils with Vitamin C; Strepsils; *Philipp.*: Strepsils; Strepsils; Therasil; *Pol.*: Neo-Angin; Strepsils; *Port.*: Benagol†; Benoral; Dropcina; Strepsils; *Rus.*: Astrasept (Астрасепт); Coldact Lorpils (Колдакт Лорпилс); Gorpils (ГОРПИЛС); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс Плюс); Strepsils with Vitamin C (Стрепсилс с Витамином С); Suprima-Lor (Суприма-Лор); Therasil (Терасил); *S.Afr.*: Strepsils Eucalyptus Menthol†; Strepsils Orange-C†; Strepsils Plus; Strepsils Soothing Honey & Lemon†; Strepsils; *Singapore*: Cofsils; Logicin Rapid Relief; Robitussin Medicated Lozenges; Strepsils Max Plus; Strepsils; *Spain*: Strepsils con Vitamina C; Strepsils Lidocaina; Strepsils; *Swed.*: Bafucin; Strepsils; *Switz.*: Anginazol; Angisan; Hextrilett†; Lidazon; Strepsils with Vitamin C; Strepsils; Sulgan N; Sulgan N; *Thai.*: Strepsils Butter Menthol Capsicum†; Strepsils Maxipluzz; Strepsils Plus Vit C; Strepsils Sugar Free†; Throatsil Plus; Throatsil; *Turk.*: Med-Angin; Strepsils C; Strepsils Mentol; Strepsils; *UK*: Strepsils with Vitamin C; Strepsils; *Ukr.*: Angi Sept Dr Theiss (Анги Септ Др Тайсс); Coldact Lor Pils (Колдакт Лор Пилс); Neo-Angin (Нео-Ангин); Rinza Lorsept (Ринза Лорсепт); Strepsils (Стрепсилс); Strepsils Plus (Стрепсилс).

Dichloroxylenol *(BAN, rINN)*

DCMX; Dichlorometaxylenol; Dichloroxylénol; Dichloroxylenolum; Dicloroxilenol; Дихлороксиленол.
2,4-Dichloro-3,5-xylenol; 2,4-Dichloro-3,5-dimethylphenol.
$C_8H_8Cl_2O$=191.1
CAS — 133-53-9.
UNII — 51AC49OLT7.

Profile

Dichloroxylenol is a chlorinated phenolic antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *India*: Haffkinol.

Multi-ingredient Preparations. *India*: Fairgenol; *UAE*: Radol.

Didecyldimethylammonium Chloride

Didecildimetilamonio, cloruro de; Didecyldimonium Chloride; Дидецилдиметиламмония Хлорид.
N-Decyl-*N*,*N*-demethyl-1-decanaminium chloride.
$C_{22}H_{48}ClN$=362.1
CAS — 7173-51-5.
ATC — D08AJ06.
ATC Vet — QD08AJ06.
UNII — JXN40O9Y98.

Profile

Didecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of the skin and mucous membranes. It is also used to disinfect instruments and surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Basix Neutral; Bio-San; *Ger.*: Amosept; Fungisept; *Ital.*: Alfa Bergamon; Bergamon In; Farmasept; Septidil.

Multi-ingredient Preparations. *Canad.*: Bio Klean; *Fr.*: Aniospray 29†; Aniosyme†; Hexanios G+R†; Surfanios†; *Ger.*: Almyrol; Freka-Nol†; Hexaquart plus; Hexaquart S; Kohrsolin extra; Kohrsolin FF; Korsolex Extra; Korsolex FF; Korsolex Plus; Lysoformin 3000; Lysoformin spezial; Meliseptol Rapid; Melsept SF; Melsitt; Mikrobac Tissues; Teta Extra†; *Ital.*: Melsept SF; *Switz.*: Desamon; *USA*: Vi Rid-Ready.

1,6-Dihydroxy-2,5-dioxahexane

Ethylene Glycol Bis(semiformal); (Ethylenedioxy)dimethanol.
[1,2-Ethanediylbis(oxy)]bismethanol.
$C_4H_{10}O_4$=122.1
CAS — 3586-55-8.

Profile

1,6-Dihydroxy-2,5,-dioxahexane is an aldehyde that slowly releases formaldehyde. It is used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Bacillol†; Kohrsolin extra; Kohrsolin†; Korsolex basic; Korsolex Extra.

Dioctyldimethylammonium Chloride

Dimethyldioctylammonium Chloride; Dioctyl Dimethyl Ammonium Chloride; Диоктилдиметиламмония Хлорид.
N,*N*-Dimethyl-*N*-octyl-1-octanaminium chloride.
$C_{18}H_{40}ClN$=306.0
CAS — 5538-94-3.

Profile

Dioctyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Vi Rid-Ready.

Dodeclonium Bromide *(rINN)*

Bromuro de dodeclonio; Dodeclonii Bromidum; Dodeclonio, bromuro de; Dodéclonium, Bromure de; GR-412; Додеклония бромид.
[2-(*p*-Chlorophenoxy)ethyl]dodecyldimethylammonium bromide.
$C_{22}H_{39}BrClNO$=448.9
CAS — 15687-13-5.
UNII — XD8BU85ZLK.

Profile

Dodecionium bromide is an antiseptic that has been included in multi-ingredient preparations intended for the treatment of skin and anorectal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Belg.*: Biogaze; *Fr.*: Dermeol; Phlebocreme; Phlebosup; Sedaplaie†; Sedorrhoide.

Domiphen Bromide *(BAN, USAN, rINN)*

Bromuro de domifeno; Domifeenibromidi; Domifenbromid; Domifeno, bromuro de; Domiphène, Bromure de; Domipheni Bromidum; NSC-39415; PDDB; Phenododecinium Bromide; Домифена Бромид.

Dodecyldimethyl-2-phenoxyethylammonium bromide.

$C_{22}H_{40}BrNO$=414.5

CAS — 13900-14-6 (domiphen); 538-71-6 (domiphen bromide).

ATC — A01AB06.

ATC Vet — QA01AB06.

UNII — R4CY19YS7C.

Pharmacopoeias. In *Br. Chin.* includes the monohydrate.

BP 2014: (Domiphen Bromide). Colourless or faintly yellow, crystalline flakes. Freely soluble in water and in alcohol; soluble in acetone.

Incompatibility. Domiphen bromide is incompatible with soaps and other anionic surfactants.

Profile

Domiphen bromide is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). Preparations containing domiphen bromide are used in the treatment of minor infections of the mouth and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Antiseptique Pastilles†; Bronchodex Pastilles†; *Gr.*: Desept; *Ital.*: Bradoral; *Malaysia*: Domidin; *Port.*: Neobradoral.

Multi-ingredient Preparations. *Austria*: Bepanthen†; Bradosol; *Canad.*: Nupercainal; *Chile*: Oralfresh; *Fr.*: Fluoselgine; *India*: Bradex-Vioform; *Ital.*: Inalar; *Pol.*: Viosept†; *Ukr.*: Viosept (Виосепт)†.

Erythorbic Acid

D-Araboascorbic Acid; E315; Erycorbin; Glucosaccharonic Acid; Isoascorbic Acid; Isovitamin C; Saccharosonic Acid; Эритробовая Кислота.

D-*erythro*-Hex-2-enoic acid γ-lactone; D-*erythro*-Hex-2-enonic acid γ-lactone.

$C_6H_8O_6$=176.1

CAS — 89-65-6.

UNII — 3113320II1.

Pharmacopoeias. In *USNF.*

USNF 31: (Erythorbic Acid). White or slightly yellow crystals or powder. It gradually darkens when exposed to light. In the dry state, it is reasonably stable in air, but in solution, it rapidly deteriorates in the presence of air. One g is soluble in about 2.5 mL of water and in about 20 mL of alcohol. Slightly soluble in glycerol. Store in airtight containers. Protect from light.

Sodium Erythorbate

E316; Sodium Isoascorbate; Sodium Isovitamin C; Эритробат Натрия.

$C_6H_7NaO_6$=198.1

CAS — 6381-77-7 (anhydrous monosodium erythorbate); 7378-23-6 (anhydrous sodium erythorbate, xNa); 63524-04-9 (monosodium erythorbate monohydrate).

UNII — BZ468R6XRD.

Profile

Erythorbic acid is the stereoisomer of L-ascorbic acid (p. 2110.3), but has little vitamin-C potency. Erythorbic acid and its sodium salt are used as antoxidants in foods and oral pharmaceutical preparations.

Ethoxyquin

Etoxiquina; Этоксихин.

6-Ethoxy-1,2-dihydro-2,2,4-trimethylquinoline.

$C_{14}H_{19}NO$=217.3

CAS — 91-53-2.

UNII — 9TT410R4OR.

Profile

Ethoxyquin has been used as an antoxidant for the prevention of common scald of apples and pears during storage and as an additive to animal feeds. Concern has been expressed over the toxicity of ethoxyquin and its residues on foodstuffs and its use is limited or restricted in some countries.

Ethylene Oxide

Dimethylene oxide; Epoxietano; 1,2-Epoxyethane; Etylenu tlenek; Óxido de etileno; Oxirane; Oxirano; Окись Этилена; Этиленоксид.

C_2H_4O=44.05

CAS — 75-21-8.

UNII — LJH7GNN18P.

Description. Ethylene oxide is a colourless flammable gas at room temperature and atmospheric pressure.

Stability. Mixtures of ethylene oxide with oxygen or air are explosive but the risk can be reduced by the addition of carbon dioxide or fluorocarbons.

Uses

Ethylene oxide is a bactericidal and fungicidal gaseous disinfectant that is effective against most micro-organisms, including viruses. It is also sporicidal. It is used for the gaseous sterilisation of heat-labile pharmaceutical and surgical materials that cannot be sterilised by other means.

Ethylene oxide forms explosive mixtures with air; this may be overcome by using mixtures containing 10% ethylene oxide in carbon dioxide, or by removing at least 95% of the air from the apparatus before admitting either ethylene oxide or a mixture of 90% ethylene oxide in carbon dioxide. Alternatively, non-flammable mixtures of dichlorodifluoromethane and trichlorofluoromethane with 9 to 12% w/w of ethylene oxide have been employed, but restrictions on the release of fluorocarbons or CFCs limit their use.

Effective sterilisation by ethylene oxide depends on exposure time, temperature, humidity, the amount and type of microbial contamination, and the partial pressure of the ethylene oxide in the exposure chamber. Concentrations of 400 to 1000 mg/litre are usually used for sterilisation and the process time may vary from 30 minutes to 10 hours. The material being sterilised must be permeable to ethylene oxide if occluded micro-organisms are present. The bactericidal action is accelerated by increase of temperature; the average temperature used is between 40 degrees and 50 degrees.

Moisture is essential for sterilisation by ethylene oxide. In practice, dry micro-organisms need to be rehydrated before ethylene oxide can be effective; humidification is normally carried out under vacuum before the introduction of ethylene oxide. Relative humidities of 40 to 60% are used.

Control of physical factors does not assure sterility, and the process should be monitored usually by using standardised suspensions of aerobic spores such as those of *Bacillus subtilis* var. *niger*.

Adverse Effects and Precautions

Ethylene oxide irritates the eyes and respiratory tract and may also cause nausea and vomiting, diarrhoea, headache, vertigo, CNS depression, dyspnoea, and pulmonary oedema. Liver and kidney damage and haemolysis may occur. Fatalities have occurred. Excessive exposure of the skin to liquid or solution causes burns, blistering, irritation, and dermatitis; percutaneous absorption may lead to systemic effects.

Many materials including plastics and rubber adsorb ethylene oxide. If such materials are being sterilised with ethylene oxide all traces of the gas must be removed before the materials can be used; removal may be by ventilation or more active means. Hypersensitivity reactions, including anaphylaxis, have been associated with ethylene oxide-contaminated materials. Ethylene oxide may also react with materials being sterilised to produce substances such as ethylene chlorohydrin (with chloride) or ethylene glycol (with water); these may contribute to any toxicity.

Pharmaceutical manufacturers within the EU have been advised to use ethylene oxide only when there is no alternative. Ethylene oxide has been shown to have carcinogenic and mutagenic properties and there is evidence of increased risk of neoplasms following occupational exposure.

Reviews.

1. WHO. Ethylene oxide. *Environmental Health Criteria 55*. Geneva: WHO, 1985. Available at: http://www.inchem.org/documents/ehc/ehc/ehc55.htm (accessed 15/03/06)
2. WHO. Ethylene oxide health and safety guide. *IPCS Health and Safety Guide 16*. Geneva: WHO, 1988. Available at: http://www.inchem.org/documents/hsg/hsg/hsg016.htm (accessed 15/03/06)
3. WHO. Ethylene oxide. *Concise International Chemical Assessment Document 54* Geneva: WHO, 2003. Available at: http://www.who.int/ipcs/publications/cicad/en/cicad54.pdf (accessed 15/03/06)

Carcinogenicity. Exposure of workers to ethylene oxide has been associated with the development of lymphatic and haematopoietic cancer and there is concern that it may be linked to breast cancer. In order to evaluate the carcinogenicity of ethylene oxide the National Institute for Occupational Safety and Health (NIOSH), in the mid 1980s, assembled a cohort of about 18 000 workers exposed to ethylene oxide.[1-3] Results of the initial cohort followed up to 1987 showed no overall excess of haematopoietic cancer, but did find a significant excess of non-Hodgkin's lymphoma among men.[1] Based on limited clinical evidence from humans and from significant evidence in *animal* studies, the IARC concluded in 1994 that there was sufficient evidence to classify ethylene oxide as a definite human carcinogen.[4] A later evaluation[3] of the NIOSH cohort from 1987 to 1998 indicated that, despite 2852 deaths as opposed to 1177 deaths in the earlier study, there was little evidence of cancer excesses for ethylene oxide exposed workers versus the general population, with the exception of bone cancer (6 deaths), and no conclusion could be drawn from this small number. However, exposure-response analyses found statistically significant evidence of an association between increased exposure and some types of haematopoietic cancer (non-Hodgkin's lymphoma and lymphocytic leukaemia), particularly for males.[2,3] There was also some evidence for a positive exposure-response for breast cancer. Follow-up of a cohort of 2876 workers exposed to ethylene oxide in the UK[5] found no statistically significant increase in mortality from cancer overall, or from any specific category of tumour. A study[6] of a cohort of 7576 female workers exposed to ethylene oxide suggested that ethylene oxide was associated with breast cancer. However, the authors indicated weaknesses in the study that could have influenced the findings.

1. Steenland K, *et al.* Mortality among workers exposed to ethylene oxide. *N Engl J Med* 1991; 324: 1402–7.
2. Stayner L, *et al.* Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. *Am J Epidemiol* 1993; 138: 787–98.
3. Steenland K, *et al.* Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998. *Occup Environ Med* 2004; 61: 2–7.
4. IARC/WHO. Some industrial chemicals. *IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans volume 60* 1994. Available at: http://monographs.iarc.fr/ENG/Monographs/vol60/volume60.pdf (accessed 23/05/06)
5. Coggon D, *et al.* Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort. *Occup Environ Med* 2004; 61: 358–62.
6. Steenland K, *et al.* Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control* 2003; 14: 531–9.

Effects on the nervous system. Four men exposed to ethylene oxide at a concentration of greater than 700 ppm developed neurological disorders. One experienced headaches, nausea, vomiting, and lethargy followed by major motor seizures. The others had headaches, limb numbness and weakness, increased fatigue, trouble with memory and thought processes, and slurred speech. Three also developed cataracts, and one required bilateral cataract extractions.[1] Rash, followed a few months later by hand numbness and weakness, headaches, and cognitive impairment, has been reported[2] in a cluster of 12 surgical nurses and technicians after exposure for 5 months to ethylene oxide-contaminated surgical gowns. Several patients showed signs of peripheral and CNS dysfunction and one patient had signs of axonal injury.

1. Jay WM, *et al.* Possible relationship of ethylene oxide exposure to cataract formation. *Am J Ophthalmol* 1982; 93: 727–32.
2. Brashear A, *et al.* Ethylene oxide neurotoxicity: a cluster of 12 nurses with peripheral and central nervous system toxicity. *Neurology* 1996; 46: 992–8.

Hypersensitivity. Anaphylactoid reactions in dialysis patients have resulted from the use of dialysis equipment sterilised with ethylene oxide.[1-3] There have also been reports of hypersensitivity[4] and anaphylactoid[5] reactions in plateletpheresis donors caused by residues of ethylene oxide in components of apheresis kits. The most common adverse reactions reported have been dyspnoea, wheezing, urticaria, flushing, headache, and hypotension, but acute severe bronchospasm, circulatory collapse, cardiac arrest, and death have also occurred. It was noted[6] that where severe, sometimes fatal, anaphylactoid reactions have occurred at the beginning of dialysis, ethylene oxide has almost universally been implicated, although exposure to cuprammonium cellulose (cuprophane) dialysis membranes may also have been involved.

It has been reported that there may be an increased risk of ethylene oxide-induced anaphylactic shock in children undergoing surgery for spina bifida.[7] Such children might be at increased risk of sensitisation and anaphylaxis, and came into frequent contact with ethylene oxide through multiple operations and catheterisations.

Occupational asthma and contact dermatitis have been attributed to residual ethylene oxide in surgical gloves.[8]

1. Bommer J, *et al.* Anaphylactoid reactions in dialysis patients: role of ethylene-oxide. *Lancet* 1985; ii: 1382–5.
2. Rumpf KW, *et al.* Association of ethylene-oxide-induced IgE antibodies with symptoms in dialysis patients. *Lancet* 1985; ii: 1385–7.
3. Röckel A, *et al.* Ethylene oxide hypersensitivity in dialysis patients. *Lancet* 1986; i: 382–3.
4. Leitman SF, *et al.* Allergic reactions in healthy plateletpheresis donors caused by sensitization to ethylene oxide gas. *N Engl J Med* 1986; 315: 1192–6.
5. Muylle L, *et al.* Anaphylactoid reaction in platelet-pheresis donor with IgE antibodies to ethylene oxide. *Lancet* 1986; ii: 1225.
6. Nicholls A. Ethylene oxide and anaphylaxis during haemodialysis. *BMJ* 1986; 292: 1221–2.
7. Moneret-Vautrin DA, *et al.* High risk of anaphylactic shock during surgery for spina bifida. *Lancet* 1990; 335: 865–6.
8. Verraes S, Michel O. Occupational asthma induced by ethylene oxide. *Lancet* 1995; 346: 1434–5.

Pregnancy. A study[1] of female staff responsible for sterilising instruments was carried out in all general hospitals in Finland. The incidence of spontaneous abortion (analysed according to employment at the time of conception and corrected for maternal age, parity, decade of pregnancy, smoking, and consumption of alcohol and coffee) was significantly increased in those exposed to ethylene oxide during pregnancy compared with those not so exposed. This study provoked criticism,[2,3] and the authors conceded that the study was not large enough to compare abortion rates and known ethylene oxide concentrations.[4] A retrospective analysis[5] of 32 dental assistants who had been exposed to ethylene oxide during pregnancy suggested that, after adjusting for age, the risk of spontaneous abortions and preterm or post-term births may have been more than doubled.

1. Hemminki K, *et al.* Spontaneous abortions in hospital staff engaged in sterilising instruments with chemical agents. *BMJ* 1982; 285: 1461–3.
2. Gordon JE, Meinhardt TJ. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; 286: 1976.
3. Austin SG. Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; 286: 1976.
4. Hemminki K, *et al.* Spontaneous abortions in hospital sterilising staff. *BMJ* 1983; 286: 1976–7.
5. Rowland AS, *et al.* Ethylene oxide exposure may increase the risk of spontaneous abortion, preterm birth, and postterm birth. *Epidemiology* 1996; 7: 363–8.

Pharmacokinetics

Ethylene oxide gas is rapidly absorbed through the lungs and distributed throughout the body. Percutaneous absorption can occur from aqueous solutions. It is rapidly metabolised by hydrolysis or conjugation with glutathione.

Ethylhexanal

2-Ethylcaproaldehyde; 2-Ethylhexylaldehyde; Octylaldehyde; Этилгексанон.

2-Ethylhexanal.

$C_8H_{16}O$=128.2

CAS — 123-05-7.

Profile

Ethylhexanal is an aldehyde disinfectant used for instrument disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Buraton 10 Ft; Helipur H plus N.

Ethylhexylglycerin

Octoxyglycerin; Этилгексиглицерин.

3-[(2-Ethylhexyl)oxy]-1,2-propanediol.

$C_{11}H_{24}O_3$=204.3

CAS — 70445-33-9.

UNII — 147D247K3P.

Profile

Ethylhexylglycerin is a disinfectant used in a concentration of 0.3% in topical deodorant preparations. It is also used in products for disinfection of the hands.

References.

1. Stausbel-Gron B, Andersen KE. Allergic contact dermatitis to ethylhexylglycerin in a cream. *Contact Dermatitis* 2007; 57: 193–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Uriage Desodorante Tri-Actif.

Formaldehyde

Formaldehid; Formaldehído; Formaldehyd; Формальдегид.

CH_2O=30.03

CAS — 50-00-0.

ATC Vet — QP53AX19.

UNII — 1HG84L3525.

Formaldehyde Solution

Formaldehído, solución de; Formaldehido tirpalas; Formaldehid-oldat; Formaldehyd roztok; Formaldéhyde, solution de; Formaldehydi solutio; Formaldehydiliuos; Formaldehydlösning; Formaldehydu roztwór.

NOTE. The names formalin and formol have been used for formaldehyde solution but in some countries they are trade marks.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Formaldehyde Solution (35 per cent); Formaldehyde Solution BP 2014). It contains 34.5 to 38.0% w/w of formaldehyde with methyl alcohol as a stabiliser. It is a clear, colourless, liquid. Miscible with water and with alcohol. It may be cloudy after storage. Store at a temperature between 15 degrees and 25 degrees. Protect from light.

USP 36: (Formaldehyde Solution). It contains not less than 34.5% w/w of formaldehyde with 9 to 15% methyl alcohol added to prevent polymerisation. It is a clear, colourless, or practically colourless liquid with a pungent, irritating odour. Miscible with water and with alcohol. Store at a temperature above 15 degrees in airtight containers. It may become cloudy on standing due to the separation of paraformaldehyde, especially if the solution is kept in a cold place; the cloudiness disappears on warming.

Strength of solutions. Formaldehyde solution is sometimes known simply as formaldehyde and this has led to confusion in interpreting the strength and the form in which formaldehyde is being used. In practice formaldehyde is available as formaldehyde solution which is diluted before use, the percentage strength being expressed in terms of formaldehyde solution rather than formaldehyde. For example, in the UK, formaldehyde solution 3% consists of 3 volumes of Formaldehyde Solution (35 Per Cent) (Ph. Eur. 8) diluted to 100 volumes with water and thus contains 1.04 to 1.14% w/w of formaldehyde; it is *not* prepared by diluting Formaldehyde Solution (35 Per Cent) (Ph. Eur. 8) to arrive at a solution containing 3% w/w of formaldehyde.

Incompatibility. Formaldehyde reacts with protein and this may diminish its antimicrobial activity.

Uses and Administration

Formaldehyde solution is a bactericidal disinfectant also effective against fungi and many viruses. It is slowly effective against bacterial spores but its sporicidal effect is greatly increased by increase in temperature.

Formaldehyde solution is usually used diluted and it is important to note that the strength of preparations is given in terms of the content of formaldehyde solution and not in terms of the final concentration of formaldehyde (see under Strength of Solutions, above).

Formaldehyde solution is used in the disinfection of blankets and bedding and in the disinfection of the membranes in dialysis equipment. It is important to ensure that there are no traces of formaldehyde on any equipment before it is used. Formaldehyde solution is also used with succinic dialdehyde for instrument disinfection.

When applied to the unbroken skin, formaldehyde solution hardens the epidermis, renders it tough and whitish, and produces a local anaesthetic effect. Diluted formaldehyde solutions, as well as a water-miscible gel containing formaldehyde 0.75% w/w, have been used for the treatment of warts on the palms of the hands and soles of the feet. Sweating of the feet may be treated by the application of formaldehyde solution in glycerol or alcohol but such applications are liable to produce sensitisation reactions and other treatments are regarded as more effective (see Hyperhidrosis, p. 1685.1).

After surgical removal of hydatid cysts, diluted formaldehyde solution has been used for irrigating the cavities to destroy scolices but other larvicides are preferred (see Echinococcosis, p. 145.2). It is generally too irritant for use on mucous membranes but it has been used in mouthwashes and pastes as an antiseptic and hardening agent for the gums. In dentistry it has been used in endodontic treatment.

Formaldehyde solution in concentrations of up to 10% v/v in saline is used as a preservative for pathological specimens. It is not suitable for preserving urine for subsequent examination. Formaldehyde solution is used for the inactivation of viruses in vaccine production.

Formaldehyde gas has little penetrating power and readily polymerises and condenses on surfaces and its efficacy depends on it dissolving in a film of moisture before acting on micro-organisms; in practice a relative humidity of 80 to 90% is necessary. Formaldehyde gas is used for the disinfection of rooms and cabinets. The gas may be produced from 500 mL of undiluted formaldehyde solution by boiling with 1 litre of water or by addition of potassium permanganate or by heating a formaldehyde-containing solid such as paraformaldehyde (p. 1763.1). Formaldehyde gas is used with low-temperature steam for the sterilisation of heat-sensitive items.

Other compounds which are thought to act by releasing formaldehyde include noxytiolin (p. 1762.1) and methenamine (p. 322.3).

Haemorrhagic cystitis. Formaldehyde has been used for local therapy of haemorrhagic cystitis (p. 2347.3), although there has been debate about the most appropriate regimen. The Fair regimen[1] for the intravesical use of formaldehyde solution in haemorrhagic cystitis involves passive irrigation of the bladder with 500 to 1000 mL of formaldehyde solution 1% v/v for a total of 10 minutes, the bladder subsequently being emptied and washed out with 1 litre of distilled water. Stronger concentrations of formaldehyde solution and other methods can be used if bleeding does not stop.[2] In a review of 118 patients treated with solutions of formaldehyde for intractable haematuria, the authors felt that this was probably the most effective treatment, but also probably the most dangerous.[3] More concentrated instillations, containing formaldehyde solution 5 to 10% seem to be generally viewed as unnecessary, and associated with an increased risk of complications which precludes their use.[4-7]

1. Fair WR. Formalin in the treatment of massive bladder hemorrhage: techniques, results, and complications. *Urology* 1974; 3: 573–6.
2. Anonymous. Haemorrhagic cystitis after radiotherapy. *Lancet* 1987; i: 304–6.
3. Godec CJ, Gleich P. Intractable hematuria and formalin. *J Urol (Baltimore)* 1983; 130: 688–91.
4. Bullock N, Whitaker RH. Massive bladder haemorrhage. *BMJ* 1985; 291: 1522–3.
5. Donahue LA, Frank IN. Intravesical formalin for haemorrhagic cystitis: analysis of therapy. *J Urol (Baltimore)* 1989; 141: 809–12.
6. Murray JA, *et al.* Massive bladder haemorrhage. *BMJ* 1986; 292: 57.
7. Smith PJB, *et al.* Massive bladder haemorrhage. *BMJ* 1986; 292: 412.

Adverse Effects and Precautions

Concentrated formaldehyde solutions applied to the skin cause whitening and hardening. Contact dermatitis and sensitivity reactions have occurred after the use of conventional concentrations and after contact with residual formaldehyde in resins.

Ingestion of formaldehyde solution causes intense burning pain in the mouth, throat, chest, and stomach, with inflammation, ulceration, and necrosis of mucous membranes. There may be nausea, vomiting, haematemesis, blood-stained diarrhoea, haematuria, and anuria; metabolic acidosis, vertigo, convulsions, loss of consciousness, and circulatory and respiratory failure may occur. Death has occurred after the ingestion of the equivalent of about 30 mL of formaldehyde solution. If the patient survives 48 hours, recovery is probable. Formaldehyde vapour is irritant to the eyes, nose, and upper respiratory tract, and may cause coughing, dysphagia, spasm and oedema of the larynx, bronchitis, pneumonia, and rarely, pulmonary oedema. Asthma-like symptoms have been reported after repeated exposure.

General references.

1. Health and Safety Executive. Formaldehyde. *Toxicity Review 2*. London: HMSO, 1981.
2. WHO. Formaldehyde. *Environmental Health Criteria 89*. Geneva: WHO, 1989. Available at: http://www.inchem.org/documents/ehc/ehc/ehc89.htm (accessed 15/03/06)
3. WHO. Formaldehyde health and safety guide. *IPCS Health and Safety Guide 57*. Geneva: WHO, 1991. Available at: http://www.inchem.org/documents/hsg/hsg/hsg057.htm (accessed 15/03/06)
4. WHO. Formaldehyde. *Concise International Chemical Assessment Document 40* Geneva: WHO, 2002. Available at: http://whqlibdoc.who.int/hq/2002/a73769.pdf (accessed 15/03/06)

Abuse. References to the abuse of embalming fluid (the primary ingredient of which is formaldehyde), usually in the form of marijuana treated with embalming fluid (street names include: dank; dip; fry; hydro; illy; sherm; wet); in some cases the embalming fluid contains phencyclidine.[1-6]

1. Holland JA, *et al.* Embalming fluid-soaked marijuana: new high or new guise for PCP? *J Psychoactive Drugs* 1998; 30: 215–9.
2. Peters RJ, *et al.* Beliefs and social norms about cigarettes or marijuana sticks laced with embalming fluid and phencyclidine (PCP): why youth use "fry". *Subst Use Misuse* 2005; 40: 563–71.

3. Singer M, *et al.* Dust in the wind: the growing use of embalming fluid among youth in Hartford, CT. *Subst Use Misuse* 2005; 40: 1035–50.
4. Singer M, *et al.* When the drug of choice is a drug of confusion: embalming fluid use in inner city Hartford, CT. *J Ethn Subst Abuse* 2005; 4: 73–96.
5. D'Onofrio G, *et al.* Lily: clinical and public health implications of a street drug. *Subst Abus* 2006; 27: 45–51.
6. Marceaux JC, *et al.* Neuropsychological effects of formaldehyde use. *J Psychoactive Drugs* 2008; 40: 207–10.

Carcinogenicity. There is controversy as to the risk formaldehyde presents as a carcinogen. Studies on the occupational exposure of medical personnel and industrial workers[1-3] to formaldehyde have generally concluded that although the risk is small or non-existent, the possibility that formaldehyde is a human carcinogen cannot be excluded. Reanalyses of some studies have led to different interpretations of the results, with some workers concluding that the risk of cancer from formaldehyde is greater than originally thought.[4] Analysis of mortality data[5] for a cohort of 25619 workers exposed to formaldehyde in the USA found some evidence of an association with nasopharyngeal cancer and possibly cancers at other upper respiratory-tract sites. Based on the results of this large cohort study and supported by evidence from other epidemiological and *animal* studies, the IARC concluded,[6] in 2004, that occupational exposure to formaldehyde does cause nasopharyngeal cancer. Furthermore, they found strong, but not sufficient, evidence to establish a causal link with leukaemia and limited evidence to suggest it causes sinonasal cancer. IARC has concluded that formaldehyde is a definite human carcinogen.[6]

1. Gérin M, *et al.* Cancer risks due to occupational exposure to formaldehyde: results of a multi-site case-control study in Montreal. *Int J Cancer* 1989; 44: 53–8.
2. Blair A, *et al.* Mortality from lung cancer among workers employed in formaldehyde industries. *Am J Ind Med* 1990; 17: 683–99.
3. Coggon D, *et al.* Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 2003; 95: 1608–15.
4. Sterling TD, Weinkam JJ. Mortality from respiratory cancers (including lung cancer) among workers employed in formaldehyde industries. *Am J Ind Med* 1994; 25: 593–602.
5. Hauptmann M, *et al.* Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 2004; 159: 1117–30.
6. IARC/WHO. Formaldehyde, 2-butoxyethanol and 1-*tert*-butoxy-2-propanol. *IARC monographs on the evaluation of carcinogenic risks to humans volume 88* 2004. Available at: http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf (accessed 23/05/06)

Effects on the blood. Haemolysis during chronic haemodialysis was due to formaldehyde eluted from filters.[1]

1. Orringer EP, Mattern WD. Formaldehyde-induced hemolysis during chronic hemodialysis. *N Engl J Med* 1976; 294: 1416–20.

Effects on the urinary tract. Adverse effects have resulted from intravesical instillation of formaldehyde solutions, ranging in strength from 1 to 10%, in the treatment of haemorrhagic cystitis. They include dysuria, suprapubic pain, ureteric and bladder fibrosis, hydronephrosis, vesicoureteral reflux, bilateral ureteral obstruction, papillary necrosis, bladder rupture, and acute tubular necrosis. Intraperitoneal spillage through a fistula, leading to adverse systemic effects, has also occurred.[1] Fatalities have resulted from cardiac arrest and acute renal failure.[1-3] See also Haemorrhagic Cystitis under Uses, p. 1752.3.

There has also been a report[4] of 4 patients exposed to high levels of atmospheric formaldehyde who developed membranous nephropathy, suggesting that there may be genetic susceptibility for this effect.

1. Capen CV, *et al.* Intraperitoneal spillage of formalin after intravesical instillation. *Urology* 1982; 19: 599–601.
2. Melekos M, Lalos J. Intravesical instillation of formalin and its complications. *Urology* 1983; 21: 331–2.
3. Sarnak MJ, *et al.* Intravesicular formaldehyde instillation and renal complications. *Clin Nephrol* 1999; 51: 122–5.
4. Breysse P, *et al.* Membranous nephropathy and formaldehyde exposure. *Ann Intern Med* 1994; 120: 396–7.

Hypersensitivity. Hypersensitivity to formaldehyde has had several manifestations. Effects on the skin have included acute exacerbation of eczema after injection of hepatitis B vaccine containing formaldehyde up to 20 micrograms/mL.[1] In another case, formaldehyde sensitivity was characterised by pruritus, burning, and redness within minutes of exposure to sunlight.[2] Painful, enlarged, and haemorrhagic gingival margins have occurred after the use of a toothpaste containing a solution of formaldehyde.[3] There is conflicting evidence of the respiratory effects of formaldehyde: although a low concentration has been reported not to trigger an asthma attack in patients with severe bronchial hyperresponsiveness,[4] occupational asthma has been documented.[5] More severe manifestations of hypersensitivity include 7 cases of shock of possible toxic or anaphylactic aetiology that occurred after the use of formaldehyde solutions during surgical removal of hydatid cysts.[6]

For mention of an allergic response to root canal paste containing paraformaldehyde, see p. 1763.1.

1. Ring J. Exacerbation of eczema by formalin-containing hepatitis B vaccine in formaldehyde-allergic patients. *Lancet* 1986; ii: 522–3.
2. Shelley WB. Immediate sunburn-like reaction in a patient with formaldehyde photosensitivity. *Arch Dermatol* 1982; 118: 117–18.
3. Laws IM. Toothpaste formulations. *Br Dent J* 1984; 156: 240.
4. Harving H, *et al.* Low concentrations of formaldehyde in bronchial asthma: a study of exposure under controlled conditions. *BMJ* 1986; 293: 310.
5. Heard BE. Low concentrations of formaldehyde in bronchial asthma. *BMJ* 1986; 293: 821.
6. Galland MC, *et al.* Risques thérapeutiques de l'utilisation des solutions de formol dans le traitement chirurgical des kystes hydatiques du foie. *Therapie* 1980; 35: 443–6.

Treatment of Adverse Effects

Contaminated skin should be washed with soap and water. After ingestion water, milk, charcoal, and/or demulcents should be given; emesis should be avoided. Assisted ventilation may be required and shock should be alleviated appropriately. Convulsions should be controlled with diazepam and pain with morphine. Acidosis, resulting from metabolism of formaldehyde to formic acid, may require intravenous sodium bicarbonate or sodium lactate. The use of haemodialysis has been suggested.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Formol†; *Ger.*: Lysoform; *Rus.*: Formagel (Формагель); Formidron (Формидрон); *UK*: Veracur; *USA*: Formadon; Formalaz; Formalyde; Lazerformaldehyde.

Multi-ingredient Preparations. *Arg.*: Cistimax Ungueal; Parodium; *Austral.*: Formo-Cresol Mitis†; *Canad.*: Duoplant†; *Chile*: Parodium; *Fr.*: Osomol; Parodium; *Ger.*: Buraton 10 F†; Incidin perfekt; Lysoformin; Melsitt; Sekusept forte S; Sporcid; Ultrasol-F; *Indon.*: Skintext†; *Ital.*: Melsept; *Rus.*: Parodium (Пародиум); Teimurov (Теймурова); *Spain*: Viberol Tirotricina.

Glucoprotamine

Glucoprotamina; Глюкопротамин.

Reaction product of L-glutamic acid and cocopropylene-1,3-diamine.

Profile

Glucoprotamine is used as a disinfectant for surfaces and medical equipment.

References.
1. Disch K. Glucoprotamine—a new antimicrobial substance. *Zentralbl Hyg Umweltmed* 1994; 195: 357–65.
2. Meyer B, Kluin C. Efficacy of glucoprotamin containing disinfectants against different species of atypical mycobacteria. *J Hosp Infect* 1999; 42: 151–4.
3. Widmer AE, Frei R. Antimicrobial activity of glucoprotamin: a clinical study of a new disinfectant for instruments. *Infect Control Hosp Epidemiol* 2003; 24: 762–4.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Incidin Plus; Sekusept Plus.

Multi-ingredient Preparations. *Ger.*: Incidin extra N; Incidin.

Glutaral *(USAN, rINN)*

Adehyd glutarowy; Glutaraldehid; Glutaraldehido; Glutaraldehyde; Glutaralum; Glutaric Dialdehyde; Pentanedial; Pentapan.

Pentane-1,5-dial.

$C_5H_8O_2$=100.1

CAS — 111-30-8.

ATC — D08AX09.

UNII — T3C89M417N.

Pharmacopoeias. Solutions of glutaral are included in *Br., Chin.*, and *US*. A solution is also in *USNF*.

BP 2014:: (Strong Glutaraldehyde Solution). It contains 47 to 53% w/w of glutaral. Store at a temperature not exceeding 15 degrees.

USP 36: (Glutaral Concentrate). It contains 50 to 52% w/w of glutaral and has a pH between 3.7 and 4.5. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

USNF 31: (Glutaral Disinfectant Solution). It has a pH between 2.7 and 3.7. Store at a temperature not exceeding 40 degrees in airtight containers. Protect from light.

Uses and Administration

Glutaral is a bactericidal disinfectant that is rapidly effective against Gram-positive and Gram-negative bacteria. It is also effective against *Mycobacterium tuberculosis*, some fungi, and viruses, including hepatitis B virus and HIV, and is slowly effective against bacterial spores. Aqueous solutions show optimum activity between pH 7.5 and 8.5; such solutions are chemically stable for about 14 days. Solutions at lower pH values are more stable.

A 2% aqueous solution buffered to a pH of about 8 (activated glutaral; alkaline glutaral) may be used for the sterilisation of endoscopic and dental instruments, rubber or plastic equipment, and for other equipment which cannot be sterilised by heat. Glutaral is non-corrosive towards most materials. Complete immersion in the solution for 10 to 20 minutes is sufficient for rapid disinfection of thoroughly cleansed instruments but exposure for up to 10 hours may be necessary for sterilisation. For further details, see Disinfection of Endoscopes, p. 1731.2, and Disinfection in Hepatitis and HIV Infection, p. 1731.2.

A 10% solution is applied twice daily for the treatment of warts (p. 1689.3); a 5% solution and a 10% gel have also been used. Glutaral should not be used for facial or anogenital warts. Glutaral has also been used topically for treating hyperhidrosis of the palms and soles, although other agents are generally preferred (see p. 1685.1).

Adverse Effects

As for Formaldehyde Solution, p. 1752.3.

Effects on the gastrointestinal tract. Insufficient rinsing of a glutaral 2% solution from flexible endoscopes after disinfection appears to be responsible for outbreaks of glutaral-induced colitis in patients undergoing colonoscopy and sigmoidoscopy.[1-4] Symptoms may occur within minutes or up to 48 hours after endoscopy and are usually abdominal pain, mucous diarrhoea, and rectal bleeding. Fever, nausea, vomiting and leucocytosis have also been reported. A case of glutaral-induced colitis has also been attributed to inadequate flushing and drying of the endoscope channels.[2]

1. Durante L, *et al.* Investigation of an outbreak of bloody diarrhea: association with endoscopic cleaning solution and demonstration of lesions in an animal model. *Am J Med* 1992; 92: 476–80.
2. West AB, *et al.* Glutaraldehyde colitis following endoscopy: clinical and pathological features and investigation of an outbreak. *Gastroenterology* 1995; 108: 1250–5.
3. Fukunaga K, Khatibi A. Glutaraldehyde colitis: a complication of screening flexible sigmoidoscopy in the primary care setting. *Ann Intern Med* 2000; 133: 315.
4. Stein BL, *et al.* Glutaraldehyde-induced colitis. *Can J Surg* 2001; 44: 113–16.

Occupational exposure. Reviews[1,2] of the occupational hazards of glutaral have noted that several studies showed adverse effects, including nausea, headache, airway obstruction, asthma, rhinitis, eye irritation, and dermatitis, occurring among medical personnel exposed to glutaral, generally at concentrations below the recommended limits. Skin reactions were due to hypersensitivity or a direct irritant effect. It was concluded that, when using glutaral, workers should take suitable precautions to protect the skin and eyes and should avoid inhaling the vapour. Appropriate procedures should also be followed for disposal and clean-up of spills.

The risk of occupational exposure to glutaral vapour may be higher in warm climates.[3]

There has also been a report of accidental ocular contact with glutaral due to leakage of glutaral solution retained in an anaesthesia mask; moderate chemical conjunctivitis ensued.[4]

1. Burge PS. Occupational risks of glutaraldehyde. *BMJ* 1989; 299: 342.
2. Ballantyne B, Jordan SL. Toxicological, medical and industrial hygiene aspects of glutaraldehyde with particular reference to its biocidal use in cold sterilization procedures. *J Appl Toxicol* 2001; 21: 131–51.
3. Mwaniki DL, Guthua SW. Occupational exposure to glutaraldehyde in tropical climates. *Lancet* 1992; 340: 1476–7.
4. Murray WJ, Ruddy MP. Toxic eye injury during induction of anaesthesia. *South Med J* 1985; 78: 1012–13.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Asepto-Glutaral; *Austral.*: Diswart; *Fr.*: Steranios†; *Ger.*: Korsolex-Endo-Disinfectant; *India*: Cadicide; Cidex; Glutihyde; *Irl.*: Glutarol; *Ital.*: Citrosteril Sterilferri; Diba; Eso H1; Ferrisepdil†; SaniSteril Sterilferri; Sporex†; *S.Afr.*: Virogerm†; *Thai.*: Glutahyde; GTR; *UK*: ASEP; Glutarol; *USA*: Cetylcide-G; Cidex.

Multi-ingredient Preparations. *Ger.*: Aerodesin; Bacillol plus; Buraton 10 F†; Helipur H plus N; Incidin perfekt; Incidur; Kohrsolin extra; Kohrsolin FF; Kohrsolin†; Korsolex basic; Korsolex Extra; Korsolex FF; Lysoformin 3000; Lysoformin; Melsept SF; Melsitt; Sekusept Extra N; Sekusept forte S; Sporcid; Ultrasol-F; *Ital.*: Citrosteril Impronte; Esoform 92; Incidin Spezial†; Melsept SF; Melsept; Sekucid†; Sekumatic†; *Rus.*: Combutec-2 (Комбутек-2); *Thai.*: Posequat with GA†.

Pharmacopoeial Preparations

BP 2014: Glutaraldehyde Solution; Strong Glutaraldehyde Solution;
USNF 31: Glutaral Disinfectant Solution;
USP 36: Glutaral Concentrate.

Glyoxal

Biformilo; Etanodial; Ethanedial; Glioxal; Oxalaldehyde; Глиоксаль.
1,2-Ethanedione.
$C_2H_2O_2$=58.04.
CAS — 107-22-2.
UNII — S0NP6LI975.

Profile

Glyoxal is an aldehyde used for the disinfection of surfaces and of medical and surgical instruments.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Buraton 10 Ft†; Freka-Nol†; Incidin perfekt; Incidur; Lysoformin 3000; Meliseptol; Melsept SF; Ultrasol-F; *Ital.*: Incidin Speział†; Indulfan†; Melsept SF; Melsept Spray; Melsept.

Halazone *(rINN)*

Halazona; Halazonum; Pantocide; Галазон.
4-(Dichlorosulphamoyl)benzoic acid.
$C_7H_5Cl_2NO_4S$=270.1.
CAS — 80-13-7.
UNII — G359OL82VB.

Pharmacopoeias. In *US.*

USP 36: (Halazone). A white crystalline powder with a characteristic odour of chlorine. Soluble 1 in more than 1000 of water and of chloroform, 1 in 140 of alcohol, and 1 in more than 2000 of ether; soluble in glacial acetic acid. It dissolves in solutions of alkali hydroxides and carbonates with the formation of a salt. Store in airtight containers. Protect from light.

Profile

Halazone is a disinfectant with the general properties of chlorine (p. 1746.2) in aqueous solution and is used for the disinfection of drinking water (p. 1731.3). It contains about 52% of 'available chlorine' (see p. 1746.3). One tablet containing 4 mg of halazone, stabilised with sodium carbonate and sodium chloride, may be sufficient to treat about 1 litre of water in about 30 minutes to 1 hour. The taste of residual chlorine may be removed by adding sodium thiosulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Helporide; *Turk.*: Haloseptil.

Pharmacopoeial Preparations
USP 36: Halazone Tablets for Solution.

Hexachlorophene *(BAN, rINN)*

G-11; Heksaklorofeeni; Hexachlorofen; Hexachlorophane; Hexachlorophène; Hexachlorophenum; Hexaclorofeno; Heksaklorofen; Гексахлорофен.
2,2'-Methylenebis(3,4,6-trichlorophenol).
$C_{13}H_6Cl_6O_2$=406.9.
CAS — 70-30-4.
ATC — D08AE01.
ATC Vet — QD08AE01; QP52AG02.
UNII — IWW5FV6NK2.

Pharmacopoeias. In *Br.* and *US.*

BP 2014: (Hexachlorophene). A white or pale buff, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol; very soluble in acetone and in ether. It dissolves in dilute solutions of alkali hydroxides. Protect from light.

USP 36: (Hexachlorophene). A white or light tan, crystalline powder which is odourless or has a slight phenolic odour. Insoluble in water; freely soluble in alcohol, in acetone, and in ether; soluble in chloroform and in dilute solutions of fixed alkali hydroxides. Store in airtight containers. Protect from light.

Incompatibility. The activity of hexachlorophene may be reduced in the presence of blood or other organic material. It retains some activity in the presence of soap.

The activity has been reported[1] to be reduced by alkaline media and by nonionic surfactants such as polysorbate 80. It is extremely sensitive to iron, and to avoid discoloration due to traces of this metal in hexachlorophene detergent solutions, it is advisable to incorporate a sequestrant such as disodium edetate.[2]

1. Walter G, Gump W. Effect of pH on hexachlorophene. *Soap Chem Spec* 1963; 39: 55–6.
2. Bell M. Hexachlorophene-based skin cleansers. *Specialities* 1965; 1: 16–18.

Uses and Administration

Hexachlorophene is a chlorinated bisphenol antiseptic with a bacteriostatic action against Gram-positive organisms, but much less effective against Gram-negative organisms. It is most active at pH 5 to 6.

Hexachlorophene is mainly used in soaps and creams in a concentration of 0.23 to 3% and is an ingredient of various preparations used for skin disorders. After repeated use of these preparations for several days there is a marked diminution of the bacterial flora due to accumulation of hexachlorophene in the skin. This residual effect is rapidly lost after washing with unmedicated soap or alcohol.

A preparation containing 3% is used for the disinfection of the hands of surgeons and other healthcare personnel. Thorough rinsing is recommended before drying. Hexachlorophene has been applied as a 0.33% dusting powder to the umbilical cord stump for the control of staphylococcal infection in the newborn. However, care is necessary when using hexachlorophene in neonates (see below).

Hexachlorophene sodium has also been used.

Disinfection. Eradication of an outbreak of infection with meticillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit was achieved by use of hexachlorophene soap for hand washing. Previous infection-control measures including the use of chlorhexidine had failed.[1] For a discussion of staphylococcal infections and their treatment, see p. 208.2.

1. Reboli AC, *et al.* Epidemic methicillin-gentamicin-resistant Staphylococcus aureus in a neonatal intensive care unit. *Am J Dis Child* 1989; 143: 34–9.

Adverse Effects and Treatment

After ingestion of hexachlorophene, anorexia, nausea, vomiting, diarrhoea, abdominal cramps, dehydration, shock, and confusion may occur. Convulsions and death may follow. CNS stimulation, convulsions, and death have also occurred after absorption of hexachlorophene from burns and damaged skin. There have been reports showing that hexachlorophene can be absorbed through the skin of infants in amounts sufficient to produce spongy lesions of the brain, sometimes fatal.

Photosensitivity and skin sensitisation have occasionally occurred after repeated use of hexachlorophene.

Treatment of adverse effects is as for Phenol, p. 1764.3.

Effects on the respiratory system. Asthma developed in a 43-year-old nurse after long-term exposure to hexachlorophene powder.[1]

1. Nagy L, Orosz M. Occupational asthma due to hexachlorophene. *Thorax* 1984; 39: 630–1.

Precautions

Hexachlorophene should not be applied to mucous membranes, large areas of skin, or to burnt, damaged, or denuded skin and should not be used vaginally, applied under occlusive dressings, or applied to areas affected by dermatoses. It should be used with caution on infants, especially premature and low birth-weight neonates. Its use is not advised in pregnancy.

Preparations of hexachlorophene are liable to contamination, especially with Gram-negative bacteria.

Breast feeding. The American Academy of Pediatrics[1] considers that, while no effects on the infant have been reported, there is a possibility of contamination of breast milk with hexachlorophene used by breast-feeding mothers for nipple washing.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Neonates. Spongiform encephalopathy has occurred in neonates who were treated topically with hexachlorophene.[1] Neonates with a birth-weight of 1.4 kg or less appeared to be most susceptible, whereas those weighing over 2 kg were not considered to be at risk.[1,2] Also most of the reports involved hexachlorophene applied in a concentration of 3%.

1. Anonymous. Hexachlorophene today. *Lancet* 1982; 1: 87–8.
2. Pluechhahn VD, Collins RB. Hexachlorophene emulsions and antiseptic skin care of newborn infants. *Med J Aust* 1976; 1: 815–19.

Pregnancy. Hexachlorophene is absorbed from the skin and crosses the placenta, but whether it has produced teratogenic effects is subject to debate.[1,2] However, it is considered best to avoid its use during pregnancy.

1. Halling H. Suspected link between exposure to hexachlorophene and malformed infants. *Ann N Y Acad Sci* 1979; 320: 426–35.
2. Baltzar B, *et al.* Pregnancy outcome among women working in Swedish hospitals. *N Engl J Med* 1979; 300: 627–8.

Pharmacokinetics

Hexachlorophene is absorbed from the gastrointestinal tract after accidental ingestion, and through intact and denuded skin. Percutaneous absorption may be significant in premature infants and through damaged skin. Hexachlorophene crosses the placenta.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Acnemask†; Incoliquid; *Indon.*: Dermisan; *Thai.*: Hexa Clean; *Venez.*: Solu-Hex.

Multi-ingredient Preparations. *Canad.*: pHisoHex; *Cz.*: Septonex; *Gr.*: Creme Phyllis de Jeunesse; Hemorrocort; Hemorroidal-H; Rysolone; *Hung.*: Phlogosol; *Indon.*: Topicide†; *Irl.*: Torbetol†; *Port.*: Anacal; *Spain*: Cresophene; *Thai.*: Cibis†; *USA*: pHisoHex; *Venez.*: Permucal.

Pharmacopoeial Preparations
BP 2014: Hexachlorophene Dusting Powder;
USP 36: Hexachlorophene Cleansing Emulsion; Hexachlorophene Liquid Soap.

Hexamidine Isetionate *(BANM, rINNM)*

Heksamidino diizetionatas; Hexamidina, isetionato de; Hexamidindiisetionat; Hexamidin-diisetionát; Hexamidindizetionát; Hexamidine Diisetionate; Hexamidine, diisétionate d'; Hexamidine Isethionate; Hexamidine, Isétionate d'; Hexamidini Diisetionas; Hexamidini Isetionas; Isetionato de hexamidina; Гексамидина Изетионат.
4,4'-(Hexamethylenedioxy)dibenzamidine bis(2-hydroxyethanesulphonate).
$C_{20}H_{26}N_4O_2.2C_2H_6O_4S$=606.7.
CAS — 3811-75-4 (hexamidine); 659-40-5 (hexamidine isetionate).
ATC — D08AC04; R01AX07; R02AA18; S01AX08; S03AA05.
ATC Vet — QD08AC04; QR01AX07; QR02AA18; QS01AX08; QS03AA05.
UNII — 023XA5Z50L.

NOTE. The name Hexamidinum has been used for primidone (p. 547.1).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hexamidine Diisetionate; Hexamidine Isetionate BP 2014). A white or slightly yellow hygroscopic powder. Sparingly soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers.

Profile

Hexamidine isetionate has antibacterial and antifungal properties and is available in preparations for the local treatment of minor infections.

Acanthamoeba keratitis. Hexamidine was suggested[1] as a possible alternative to propamidine for the treatment of *Acanthamoeba* keratitis (p. 919.3) due to the poor cysticidal activity, chronic conjunctival infection, and resistance of some *Acanthamoeba* strains seen with propamidine.[1,2] Cures have been reported with 0.1% hexamidine used either as monotherapy[2,3] or with polihexanide.[2]

1. Perrine D, *et al.* Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; 39: 339–42.
2. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; 26: 231–6.
3. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; 17: 893–905.

Adverse effects. A systemic allergic reaction in a patient after use of a topical antiseptic cream was confirmed, by skin prick tests, to be caused by hexamidine.[1]

1. Mullins RJ. Systemic allergy to topical hexamidine. *Med J Aust* 2006; 185: 177.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Desomedine; Hexomedine; Ophtamedine; *Fr.*: Desomedine; Hexaseptine; Hexomedine; *Ger.*: Laryngomedin N†; *Gr.*: Ophtamedine; *Singapore*: Desomedine; *Switz.*: Desomedine; *Venez.*: Hexomedine.

Multi-ingredient Preparations. *Austral.*: Medi Creme; Medi Pulv; *Austria*: Imazol Duo; *Belg.*: Colludol; Hexomedine†; *Braz.*: Hexomedine; *Cz.*: Cyteal; Imacort; Imazol Plus; *Fr.*: Aurigoutte; Colludol; Cyteal; Doli Mal de Gorge; Ergix mal de gorge; Oto-

mide†; Solutricine Maux de Gorge†; *Ger.*: Imazol comp; Imazol Plus; *Gr.*: Octrene; Pulvo-Hexa; ***Hong Kong***: Medicreme†; ***Neth.***: Imazol Duo; *NZ*: Medicreme†; Medipulv; ***Philipp.***: Cyteal; ***Pol.***: Imazol Plus; ***Port.***: Cyteal; ***Rus.***: Cyteal (Цитеал); ***Singapore***: Cyteal; ***Spain***: Tantum†; ***Switz.***: Imacort; Imazol; ***Thai.***: Pulvo 47†; ***Turk.***: Imazol; Pulvo 47; *UK*: Cyteal; ***Ukr.***: Cyteal (Цитеал); Imacort (Имакорт).

Hexetidine *(BAN, rINN)*

Heksetidiini; Heksetidin; Heksetidinas; Hexetidin; Hexetidina; Hexétidine; Hexetidinum; Гексэтидин.

5-Amino-1,3-bis(2-ethylhexyl)hexahydro-5-methylpyrimidine.

$C_{21}H_{45}N_3$=339.6

CAS — 141-94-6.

ATC — A01AB12.

ATC Vet — QA01AB12.

UNII — 852A84Y8LS.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Hexetidine). An oily, colourless or slightly yellow liquid. Very slightly soluble in water; very soluble in alcohol, in acetone, and in dichloromethane. It dissolves in dilute mineral acids. Protect from light.

Uses and Administration

Hexetidine is a bactericidal and fungicidal antiseptic. It is used for minor infections of mucous membranes, and in particular as a 0.1% mouthwash for local infections and oral hygiene.

Oral hygiene. A mouthwash containing 0.1% hexetidine was no more effective than placebo in the management of patients with aphthous ulceration (see Mouth Ulceration, p. 1811.2) and provided no additional benefits to oral hygiene or gingival health.[1] However, such a mouthwash does appear to be of benefit in reducing supragingival plaque and gingival inflammation.[2]

1. Chadwick B, *et al.* Hexetidine mouthrinse in the management of minor aphthous ulceration and as an adjunct to oral hygiene. *Br Dent J* 1991; 171: 83–7.
2. Sharma NC, *et al.* Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash. *J Clin Periodontol* 2003; 30: 590–4.

Adverse Effects

Allergic contact dermatitis, alterations in taste, and transient anaesthesia have occasionally been reported.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Arg.***: Duranil; ***Austria***: Hexoral; ***Belg.***: Hextril; ***Canad.***: Steri/Sol; ***Chile***: Duranil; ***Fr.***: Collu-Hextril; Hextril; ***Ger.***: Hexoral; Vagi-Hex; ***Gr.***: Hexalen; Hexalyse; Irin; ***Hong Kong***: Bactidol; ***Indon.***: Bactidol†; ***Hexadol***; ***Irl.***: Oraldene; ***Ital.***: Actiseptic; ***Malaysia***: Hexadol; ***Neth.***: Hextril; ***Philipp.***: Bactidol; Vagi-Hex; ***Port.***: Collu-Hextril; Hextril; ***Rus.***: Hexoral (Гексорал); Stomatidine (Стоматидин); ***S.Afr.***: Oraldine; ***Singapore***: Bactidol; ***Switz.***: Drossadin; Hextril; Vagi-Hex; ***Turk.***: Heksoral; Hekzoton; Vagi-Hex; ***UK***: Oraldene; ***Ukr.***: Hexoral (Гексорал); Stomatidin (Стоматидин).

Multi-ingredient Preparations. ***Arg.***: Buchex; Mantus; ***Austria***: Gurfix†; Isozid-H; ***Belg.***: Givalex; ***Cz.***: Stopangin; Stopangin; ***Fr.***: Angispray; Givalex; ***Hong Kong***: Anso; ***Ital.***: Neo Emoform; ***Rus.***: Stopangin (Стопангин); ***Spain***: Abrasone Rectal; Mentamida†; ***Ukr.***: Angilex (Ангилекс); Givalex (Гивалекс); Heppylor (Хеппилор); Stopangin (Стопангин); Stopangin (Стопангин).

Hexylresorcinol *(BAN)*

Esilresorcina; Heksilrezorcinolis; Heksyyliresorsinoli; Hexilresorcinol; Hexilrezorcin; Hexylresocinolum; Hexylresorc; Hexylresorcin; Hexylrésorcinol; Hexylresorcinolum; Гексилрезорцин.

4-Hexylbenzene-1,3-diol.

$C_{12}H_{18}O_2$=194.3

CAS — 136-77-6.

ATC — R02AA12.

ATC Vet — QR02AA12.

UNII — R9QTB5E82N.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Hexylresorcinol). A colourless, yellowish or reddish crystalline powder or needles, turning brownish-pink on exposure to light or air. It exhibits polymorphism. M.p. 66 degrees to 68 degrees; melting may occur at about 60 degrees followed by solidification and a second melting at 66 degrees to 68 degrees. Very slightly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 36: (Hexylresorcinol). M.p. 62 degrees to 67 degrees. Store in airtight containers. Protect from light.

Incompatibility. Hexylresorcinol is incompatible with alkalis and oxidising agents.

Profile

Hexylresorcinol is a phenolic antiseptic that is used topically for the treatment of minor infections of the skin and mucous membranes, and in the form of lozenges for the treatment of sore throat. It has also been used in vaginal spermicidal preparations.

High concentrations of hexylresorcinol are irritant and corrosive to skin and mucous membranes. Alcoholic solutions are vesicant.

It was formerly used as an anthelmintic.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. ***Austral.***: Strepsils Extra†; ***Canad.***: Antiseptic Throat Lozenges; Bradosol; Bronchodex Pastilles Antiseptiques†; Soothe Aid; Strepsils Anesthetic Formula; Sucrets Extra Strength; *Cz.*: Strepsinol†; ***Hong Kong***: Strepsils Pain Relief; ***Irl.***: Strepsils Extra; ***Malaysia***: Strepsils Max; Strepsils Pain Relief†; ***Singapore***: Strepsils Max; ***UK***: Halls Soothers Triple Action; Lemsip Sore Throat; Soothers Triple Action; Strepsils Extra; TCP; ***USA***: ST 37; Sucrets Original Formula Sore Throat Original Mint.

Multi-ingredient Preparations. ***Arg.***: Algiodent; Balsamina; Caramelos Antibioticos Lefmar; Caramelos Antibioticos; Caramelos Oriental; Collubiazol; Dorrin; Fanaletas; Fungicida; Gargadrin-R; Ixana; No-Tos Adultos; No-Tos Pocket; Pastillas Medex; Refenax Caramelos Expectorantes; Suavisan N; ***Braz.***: Andriodermol; Andriodermol; ***Canad.***: Strepsils Extra; ***Chile***: Fittig Antimicotico; *Cz.*: Coldrex Proti Bolesti v Krku; ***Hong Kong***: Dequasin; ***India***: Tytin; ***Pol.***: Cholisept Intensive; Coldrex†; ***UK***: Beechams Max Strength Sore Throat Relief; Beechams Throat-Plus.

Pharmacopoeial Preparations

USP 36: Hexylresorcinol Lozenges.

Hydrargaphen *(BAN, rINN)*

Hidrargafeno; Hydraphen; Hydrargaphène; Hydrargaphenum; Hygraphen; Phenylmercuric Dinaphthylmethanedisulfonate; Гидраграфен.

μ-(2,2′-Binaphthalene-3-sulphonyloxy)bis(phenylmercury).

$C_{33}H_{24}Hg_2O_6S_2$=981.9

CAS — 14235-86-0.

UNII — DL2D409P9O.

Profile

Hydrargaphen is a mercurial antiseptic with antibacterial and antifungal properties. It has been used as a pesticide.

Hydrogen Peroxide

Hidrojen Peroksit; Hydrogène, peroxyde d'; Hydrogenii Peroxidum; Peróxido de hidrógeno; Перекись Водорода.

H_2O_2=34.01

CAS — 7722-84-1.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

UNII — BBX060AN9V.

NOTE. The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Incompatibility. Hydrogen peroxide solutions are incompatible with reducing agents, including organic matter and oxidisable substances, and with some metals, metallic salts, alkalis, iodides, permanganates, and other stronger oxidising agents.

Stability. Aqueous solutions of hydrogen peroxide gradually decompose on standing and if allowed to become alkaline. Decomposition is increased by light, agitation, and heat. Incompatibility may also produce decomposition. Solutions are comparatively stable in the presence of a slight excess of acid. Strong solutions are considered to be more stable than weak solutions.

Storage. Solutions of hydrogen peroxide should be stored in airtight containers at 15 degrees to 30 degrees (but see Hydrogen Peroxide Solution (30 per cent), below). Solutions should not be stored for long periods. Those not containing a stabiliser should be stored at a temperature not exceeding 15 degrees. Protect from light.

Hydrogen Peroxide Solution (3 per cent)

3%-os hidrogén-peroxid-oldat; Agua oxigenada (10 volúmenes); Dilute Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (10-volume); Hydrogen Peroxide Topical Solution; Hydrogenii Peroxidum 3%; Hydrogenii Peroxidum 3 Per Centum; Oxydol; Peroxid vodíku 3%; Peróxido de hidrógeno, solución al 3%; Vandenilio peroksido 3% tirpalas; Väteperoxid 3%; Vetyperoksidi 3%; Wasserstoffperoxid-Lösung 3 %; Wodoru nadtlenek 3%.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Hydrogen Peroxide Solution (3 per cent)). A clear colourless liquid containing 2.5 to 3.5% w/w of H_2O_2 corresponding to about 10 times its volume of oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

USP 36: (Hydrogen Peroxide Topical Solution). It contains 2.5 to 3.5% w/v of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. Store in airtight containers at a temperature between 15 degrees and 30 degrees. Protect from light.

Hydrogen Peroxide Solution (6 per cent)

Hydrog. Perox. Soln; Hydrogen Dioxide Solution; Hydrogen Peroxide Solution; Hydrogen Peroxide Solution (20-volume); Liq. Hydrog. Perox.; Liquor Hydrogenii Peroxidi; Peróxido de hidrógeno, solución al 6%; Solución de Bióxido de Hidrogeno; Soluté Officinal d'Eau Oxygénée; Wasserstoffsuperoxydlösung.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Br.*

BP 2014: (Hydrogen Peroxide Solution (6 per cent)). A clear colourless aqueous liquid containing 5.0 to 7.0% w/v of H_2O_2 corresponding to about 20 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. It should not be stored for long periods. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (27 per cent)

Hydrogenii Peroxidum; Perossido d'Idrogeno Soluzione; Peróxido de hidrógeno, solución al 27%; Solutio Hydrogenii Peroxydati; Strong Hydrog. Perox. Soln; Strong Hydrogen Peroxide Solution.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Description. Hydrogen peroxide solution (27 per cent) is a clear, colourless aqueous solution containing 26 to 28% w/w of H_2O_2, corresponding to about 100 times its volume of available oxygen. It may contain a suitable stabilising agent.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

Hydrogen Peroxide Solution (30 per cent)

30%-os hidrogén-peroxid-oldat; Hydrogen Peroxide Concentrate; Hydrogen Peroxide Solution (100-volume); Hydrogenii Peroxidum 30%; Hydrogenii Peroxidum 30 Per Centum; Peroxid vodíku 30%; Peróxido de hidrógeno, solución al 30%; Vandenilio peroksido 30% tirpalas; Väteperoxid 30%; Vetyperoksidi 30%; Wasserstoffperoxid-Lösung 30 %; Wodoru nadtlenek 30%.

ATC — A01AB02; D08AX01; S02AA06.

ATC Vet — QA01AB02; QD08AX01; QS02AA06.

Pharmacopoeias. In *Eur.* (see p. vii).

Chin. specifies 26 to 28%.

US and *Viet.* specify 29 to 32%.

Ph. Eur. 8: (Hydrogen Peroxide Solution (30 per cent)). A clear colourless liquid containing 29.0 to 31.0% w/w of H_2O_2 corresponding to about 110 times its volume of available oxygen. It decomposes in contact with oxidisable organic matter and with certain metals and if allowed to become alkali. It may contain a suitable stabilising agent. Solutions not containing a stabilising agent should be stored at a temperature below 15 degrees. Protect from light.

The BP 2014 directs that when Hydrogen Peroxide is prescribed or demanded, Hydrogen Peroxide Solution (6 per cent) shall be dispensed or supplied.

USP 36: (Hydrogen Peroxide Concentrate). A clear, colourless liquid containing 29 to 32% w/w of H_2O_2. It may contain up to 0.05% of a suitable preservative or preservatives. It is acid to litmus. It slowly decomposes and is affected by light. Store in partially-filled containers having a small vent in the closure, at a temperature of 8 degrees to 15 degrees.

Uses and Administration

Hydrogen peroxide is an oxidising agent used as an antiseptic, disinfectant, and deodorant. It has weak antibacterial activity and is also effective against viruses, including HIV. It also has a mild haemostatic action. It owes its antiseptic action to its ready release of oxygen when applied to tissues, but the effect lasts only as long as the oxygen is being released and is of short duration; in addition the antimicrobial effect of the liberated oxygen is reduced in the presence of organic matter. The mechanical effect of effervescence is probably more useful for wound cleansing (p. 1732.2) than the antimicrobial action.

Hydrogen peroxide solutions are used to cleanse wounds and ulcers in concentrations of up to 6%; creams containing 1 or 1.5% stabilised hydrogen peroxide are also used. Although hydrogen peroxide alone is not considered effective on intact skin, it is used with other antiseptics for the disinfection of hands, skin, and mucous membranes. Injection into closed body cavities is dangerous (see below). Adhering and blood-soaked dressings may be released by the application of a solution of hydrogen peroxide.

A 1.5% solution of hydrogen peroxide has been used as a mouthwash in the treatment of acute stomatitis and as a deodorant gargle. A suitable solution can be prepared by diluting 15 mL of hydrogen peroxide 6% in half a tumblerful of warm water. An oral gel has also been used.

Hydrogen peroxide ear drops have been used for the removal of wax. Such ear drops were prepared by diluting a 6% solution of hydrogen peroxide with 3 parts of water preferably just before use.

Hydrogen peroxide 3% is used for disinfecting soft contact lenses.

Immersion for 30 minutes in hydrogen peroxide 6% has been suggested for disinfecting cleaned equipment.

For bleaching hair and delicate fabrics hydrogen peroxide 6% should be diluted with an equal volume of water.

Strong solutions (27 per cent and 30 per cent) of hydrogen peroxide are used for the preparation of weaker solutions and should not be applied to tissues undiluted.

Hydrogen peroxide and other peroxides have many industrial uses as bleaching and oxidising agents.

Disinfection. *CONTACT LENSES.* Hydrogen peroxide 3% is particularly useful for disinfecting soft contact lenses (p. 1730.2) and lens storage cases since it is effective against *Acanthamoeba* spp. However, it is irritant to the cornea and requires inactivating with sodium pyruvate, catalase, or sodium thiosulfate, or with a platinum catalyst, before the lenses are used.

DIALYSIS EQUIPMENT. A disinfectant containing hydrogen peroxide and peracetic acid (*Renalin*) was not completely effective in killing *Mycobacterium chelonae* in high-flux dialysers. This possibly led to infection of 5 dialysis patients.[1] For a report of haemolysis and methaemoglobinaemia after inadvertent contamination of dialysis fluid with hydrogen peroxide, see Intravascular Administration under Adverse Effects and Precautions, below.

1. Lowry PW, *et al.* Mycobacterium chelonae infection among patients receiving high-flux dialysis in a hemodialysis clinic in California. *J Infect Dis* 1990; 161: 85–90.

ENDOSCOPES. Peroxygen compounds have been suggested for disinfection of endoscopes as an alternative to glutaral (p. 1731.2). In the USA, a product containing 7.5% hydrogen peroxide is available as a high level disinfectant for processing of reusable medical devices.[1] Products containing varying concentrations of hydrogen peroxide with peracetic acid have also been approved by the FDA.

Hydrogen peroxide damages external surfaces, particularly rubbers and plastics of the insertion tubes and can corrode aluminium, nickel-silver alloy, and chrome. It is not considered suitable for flexible endoscopes.[2] Other peroxygen-containing compounds have been assessed for disinfecting endoscopes, but they appear to be less active against enteroviruses[3] and mycobacteria.[4] The Working Party of the British Society of Gastroenterology does not recommend peroxygen disinfectants for gastrointestinal endoscopes, unless a hydrogen peroxide gas plasma system is used during the sterilisation of invasive flexible endoscopes.[5]

Residual hydrogen peroxide solution can cause mucosal damage (see Closed Body Cavities, under Adverse Effects and Precautions, below) and endoscopes should be thoroughly rinsed before use.

1. FDA. FDA-cleared sterilants and high level disinfectants with general claims for processing reusable medical and dental devices (issued May 13, 2005). Available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ReprocessingofSingle-UseDevices/ucm133514 (accessed 06/04/10)
2. Society of Gastroenterology Nurses and Associates, Inc. Guideline for use of high level disinfectants and sterilants for reprocessing flexible gastrointestinal endoscopes (issued 2006). Available at: http://www.sgna.org/Resources/hldguidelinefinal2007v3.pdf (accessed 13/05/10)
3. Tyler R, *et al.* Virucidal activity of disinfectants: studies with the poliovirus. *J Hosp Infect* 1990; 15: 339–45.
4. Broadley SJ, *et al.* Antimycobacterial activity of 'Virkon'. *J Hosp Infect* 1993; 23: 189–97.
5. British Society of Gastroenterology. BSG Working Party Report 2008. BSG guidelines for decontamination of equipment for gastrointestinal endoscopy. Available at: http://www.bsg.org.uk/images/stories/docs/clinical/guidelines/endoscopy/decontamination_2008.pdf (accessed 26/02/10)

Mouth ulceration and infection. The use of antiseptic mouthwashes may be helpful in the management of mouth ulcers (p. 1811.2), although the use of high concentrations of hydrogen peroxide is not advisable (see Effects on the Mouth, below). Application of a 1.5% solution to individual ulcers with a topical corticosteroid may be useful. A randomised placebo-controlled study[1] to test the efficacy of a 1.5% hydrogen peroxide and 0.05% sodium fluoride-based mouthwash on gingivitis and tooth whitening, over a 6-month period found that it effectively whitened teeth and significantly reduced gingival redness. However, a review of the literature with practice guidelines pertaining to oral care of the critically ill[2] concluded that hydrogen peroxide could not be recommended as a mouthwash in this group, due to lack of evidence regarding its safety and efficacy in critically ill patients. A hydrogen peroxide denture cleaner was not effective in either preventing re-infection or in reducing mucosal inflammation in a study of 49 patients.[3] For oral candidal infections, specific antifungals are recommended (see p. 564.1).

1. Hasturk H, *et al.* Efficacy of a fluoridated hydrogen peroxide-based mouthrinse for the treatment of gingivitis: a randomized clinical trial. *J Periodontol* 2004; 75: 57–65.
2. O'Reilly M. Oral care of the critically ill: a review of the literature and guidelines for practice. *Aust Crit Care* 2003; 16: 101–10.
3. Walker DM, *et al.* The treatment of denture-induced stomatitis: evaluation of two agents. *Br Dent J* 1981; 151: 416–19.

Adverse Effects and Precautions

Strong solutions of hydrogen peroxide produce irritating 'burns' on the skin and mucous membranes with a white eschar, but the pain disappears in about an hour. Continued use of hydrogen peroxide as a mouthwash may cause reversible hypertrophy of the papillae of the tongue.

It is dangerous to inject or instil hydrogen peroxide into closed body cavities from which the released oxygen has no free exit. Colonic lavage with solutions of hydrogen peroxide has been followed by gas embolism, rupture of the colon, proctitis, ulcerative colitis, and gangrene of the intestine.

Closed body cavities. Liberation of oxygen during the use of hydrogen peroxide in surgical procedures has resulted in oxygen embolism and local emphysema.[1-3] Gas embolism has also been reported after accidental ingestion of hydrogen peroxide solution.[4] Local damage to the colonic and rectal mucosa has followed the use of hydrogen peroxide 3% as an enema[5,6] and from residual hydrogen peroxide after disinfection of endoscopes.[7]

1. Sleigh JW, Linter SPK. Hazards of hydrogen peroxide. *BMJ* 1985; 291: 1706.
2. Saissy JM, *et al.* Risques de l'irrigation au peroxyde d'hydrogène en chirurgie de guerre. *Ann Fr Anesth Reanim* 1994; 13: 749–53.
3. Konrad C, *et al.* Pulmonary embolism and hydrogen peroxide. *Can J Anaesth* 1997; 44: 338–9.
4. Rackoff WR, Merton DF. Gas embolism after ingestion of hydrogen peroxide. *Pediatrics* 1990; 85: 593–4.
5. Auroux J, *et al.* Rectocolite aiguë iatrogène après lavement à l'eau oxygénée. *Rev Geriatr* 1997; 22: 21–4.
6. Gan SI, Price LM. Waiting-list induced proctitis: the hydrogen peroxide enema. *Can J Gastroenterol* 2003; 17: 727–9.
7. Ryan CK, Potter GD. Disinfectant colitis: rinse as well as you wash. *J Clin Gastroenterol* 1995; 21: 6–9.

Effects on the mouth. Use of hydrogen peroxide 3% as a mouthwash has been reported to cause mouth ulceration. A review[1] on the safety of hydrogen peroxide in dentistry concluded that low concentrations of hydrogen peroxide (1.5 to 3%) used long-term in mouthwashes and dentifrices, resulted in no adverse changes to the hard or soft tissues in the mouth. However, irritation may occur with low concentrations in patients with a thin or ulcerated oral mucosa. Short-term exposure to higher concentrations (30 to 35%), such as those used in teeth bleaching products and procedures, have resulted in mucosal erythema and sloughing, while long-term exposure may cause inflammation or hyperplasia.

1. Walsh LJ. Safety issues relating to the use of hydrogen peroxide in dentistry. *Aust Dent J* 2000; 45: 257–69.

Intravascular administration. Intravenous injection of hydrogen peroxide solutions as unconventional therapy for AIDS or cancer has resulted in severe acute haemolysis.[1,2] Haemolysis and methaemoglobinaemia have been reported due to contamination of haemodialysis fluid with hydrogen peroxide.[3,4]

1. Jordan KS, *et al.* A 39-year-old man with acute hemolytic crisis secondary to intravenous injection of hydrogen peroxide. *J Emerg Nurs* 1991; 17: 8–10.
2. Hirschtick RE, *et al.* Death from an unconventional therapy for AIDS. *Ann Intern Med* 1994; 120: 694.
3. Gordon SM, *et al.* Hemolysis associated with hydrogen peroxide at a pediatric dialysis center. *Am J Nephrol* 1990; 10: 123–7.
4. Davidovits M, *et al.* Methaemoglobinaemia and haemolysis associated with hydrogen peroxide in a paediatric haemodialysis centre: a warning note. *Nephrol Dial Transplant* 2003; 18: 2354–8.

Poisoning. Ingestion of small quantities of hydrogen peroxide 3% generally results in only mild gastrointestinal effects. Ingestion of solutions of 10% or greater or large quantities of 3% solutions have been associated with severe morbidity and mortality. Irritation of the gastrointestinal tract with nausea, vomiting, foaming at the mouth, and haematemesis may occur. Blistering of the mucosa or oropharyngeal burns are common with solutions of 30% or greater. Large volumes of oxygen gas are produced in the stomach and this may result in painful gastric distension and belching. Apnoea, coma, convulsions, confusion, cyanosis, lethargy, stridor, and cardiorespiratory arrest have also been reported. Oxygen gas embolism is particularly dangerous. Immediate and permanent neurological damage has been reported after ingestion of hydrogen peroxide 35% and deaths have been reported in children and adults. Inhalation of high concentrations of hydrogen peroxide may cause irritation of the mucous membranes causing coughing and dyspnoea. Shock, convulsions, pulmonary oedema, and coma may follow. Exposure of the skin to concentrated solutions of hydrogen peroxide has resulted in blistering, erythema, focal epidermal necrosis, and purpura. Concentrations above 10% may result in ulceration or perforation of the cornea if they enter the eyes.[1]

1. Watt BE, *et al.* Hydrogen peroxide poisoning. *Toxicol Rev* 2004; 23: 51–7.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies hydrogen peroxide as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 24/10/11)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Aosept Plus; Oxysept Comfort; ***Austral.***: Aosept; Focus Care One Step†; Oxysept 1 Step; Peroxyl; *Belg.*: Confosept Zuurstofwater; *Braz.*: Oxysept†; *Canad.*: Aosept; Butcher's Per Diem; Orajel Perioseptic†; Oxysept; Pero Vap; Perox-A-Mint†; Peroxyl; *Denm.*: Microcid; *Fr.*: Dentex; Dosoxygenee; *Ger.*: Crystacide; *Gr.*: Biosept†; Crystacide; Peroxyl; *Irl.*: Hioxyl†; *Ital.*: Crystacide; Oragard†; *Norw.*: Microcid; *NZ*: Aosept; Crystacide; *Pol.*: Peroxy-Dental; Peroxygel; *Port.*: Crystacide; *Rus.*: Parkon (Паркон); *Singapore*: Pineapple Brand Ear Drop; *Swed.*: Microcid; *Turk.*: Oksijenli; Perohid; *UK*: Crystacide; Peroxyl; *USA*: Aosept; MiraSept†; Oxysept†; Peroxyl.

Multi-ingredient Preparations. *Arg.*: Arion Cronos; ***Austria***: Kodan; Skinsept mucosa†; *Braz.*: Malvatricin Branqueador†; *Canad.*: Actril; UltraCare†; *Fr.*: Anioxyde†; *Ger.*: AdaptaCide PAA-C; Skinsept P; Skinsept mucosa; *Indon.*: Spitaderm†; *Ital.*: Eso 70; Peresal†; Spitaderm†; *Neth.*: Spitaderm†; *NZ*: Oxysept 1 Step; *Singapore*: Clearasil Ultra Spot Clearing Cream; *Spain*: Oximen; *USA*: Soft Mate Consept; UltraCare.

Pharmacopoeial Preparations
BP 2014: Hydrogen Peroxide Mouthwash;
USP 36: Hydrogen Peroxide Topical Solution.

Hydroxybenzoates

p-Hidroxibenzoatos; Parabenos; Parabens; Parahidroxibenzoatos; Гидроксибензоаты.

Benzyl Hydroxybenzoate

Benzyl Parahydroxybenzoate; Benzylparaben; Parahidroxibenzoato de bencilo; Бензил Гидроксибензоат.

Benzyl 4-hydroxybenzoate.

$C_{14}H_{12}O_3$=228.2.

CAS — 94-18-8.

UNII — 8Y41DYV4VG.

Pharmacopoeias. In *Br.* and *Int.*

BP 2014: (Benzyl Hydroxybenzoate). A white to creamy-white, odourless or almost odourless, crystalline powder. Practically insoluble in water; freely soluble in alcohol and

in ether. It dissolves in solutions of alkali hydroxides. M.p. about 112 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Butyl Hydroxybenzoate

Butilo parahidroksibenzoatas; Butilparabeno; Butil-parahidroxi-benzoát; Butyl Parahydroxybenzoate; Butyle, parahydroxybenzoate de; Butyl-4-hydroxybenzoat; Butylis Parahydroxybenzoas; Butylis Paraoxybenzoas; Butylparaben; Butylparabenum; Butylparahydroxibensoat; Butylu parahydroksybenzoesan; Butyyliparahydroksibentsoaatti; Parahidroxibenzoato de butilo; Бутил Гидроксибензоат.

Butyl 4-hydroxybenzoate.

$C_{11}H_{14}O_3$=194.2

CAS — 94-26-8.

UNII — 3QPI1U3FV8.

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Butyl Parahydroxybenzoate; Butyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 68 degrees to 71 degrees.

USNF 31: (Butylparaben). Small colourless crystals or a white powder. Very slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol. M.p. 68 degrees to 71 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Ethyl Hydroxybenzoate

Aethylum Hydroxybenzoicum; E214; Ethyl Parahydroxybenzoate; Éthyle, parahydroxybenzoate d'; Ethyl-4-hydroxybenzoat; Ethylis parahydroxybenzoas; Ethylis Paraoxybenzoas; Ethylparaben; Ethylparabenum; Etilo parahidroksibenzoatas; Etilparabeno; Etil-parahidroxibenzoát; Etylparahydroxibensoat; Etylu parahydroksybenzoesan; Etyyliparahydroksibentsoaatti; Parahidroxibenzoato de etilo; Этил Гидроксибензоат.

Ethyl 4-hydroxybenzoate.

$C_9H_{10}O_3$=166.2

CAS — 120-47-8.

ATC — D01AE10.

ATC Vet — QD01AE10.

UNII — 14255EXE39.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Ethyl Parahydroxybenzoate; Ethyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol.

USNF 31: (Ethylparaben). Small colourless crystals or a white powder. Slightly soluble in water and in glycerol; freely soluble in alcohol, in acetone, in ether, and in propylene glycol.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Methyl Hydroxybenzoate

E218; Metagin; Methyl Parahydroxybenzoate; Méthyle, parahydroxybenzoate de; Methyl-4-hydroxybenzoat; Methylis Oxybenzoas; Methylis parahydroxybenzoas; Methylis Paraoxibenzoas; Methylparaben (USAN); Methylparabenum; Metilo parahidroksibenzoatas; Metilparabeno; Metil-parahidroxibenzoát; Metylparahydroxibensoat; Metylu parahydroksybenzoesan; Metyyliparahydroksibentsoaatti; Parahidroxibenzoato de metilo; Метил Гидроксибензоат.

Methyl 4-hydroxybenzoate.

$C_8H_8O_3$=152.1.

CAS — 99-76-3.

UNII — A2I8C7HI9T.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Methyl Parahydroxybenzoate; Methyl Hydroxybenzoate BP 2014). Colourless crystals or a white or almost white crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 125 degrees to 128 degrees.

USNF 31: (Methylparaben). Colourless crystals or a white crystalline powder. Soluble 1 in 400 of water, 1 in 50 of water at 80 degrees, 1 in 3 of alcohol, and 1 in 10 of ether; freely soluble in methyl alcohol. M.p. 125 degrees to 128 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Propyl Hydroxybenzoate

E216; Parahidroxibenzoato de propilo; Propagin; Propilo parahidroksibenzoatas; Propilparabeno; Propil-parahidroxibenzoát; Propyl Parahydroxybenzoate; Propyle, parahydroxybenzoate de; Propyl-4-hydroxybenzoat; Propylis Oxybenzoas; Propylis Parahydroxybenzoas; Propylis Paraoxibenzoas; Propylparaben (USAN); Propylparabenum; Propylparahydroxibensoat; Propylu parahydrobenzoesan; Propylu parahydroksybenzoesan; Propyyliparahydroksibentsoaatti; Пропил Гидроксибензоат.

Propyl 4-hydroxybenzoate.

$C_{10}H_{12}O_3$=180.2

CAS — 94-13-3.

UNII — Z8IX2SC1OH.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Propyl Parahydroxybenzoate; Propyl Hydroxybenzoate BP 2014). A white or almost white, crystalline powder. Very slightly soluble in water; freely soluble in alcohol and in methyl alcohol. M.p. 96 degrees to 99 degrees.

USNF 31: (Propylparaben). Small colourless crystals or a white powder. Soluble 1 in 2500 of water, 1 in 400 of boiling water, 1 in 1.5 of alcohol, and 1 in 3 of ether. M.p. 96 degrees to 99 degrees.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Butyl Hydroxybenzoate

Butilparabeno sódico; *p*-Hidroxibenzoato sódico de butilo; Parahidroxibenzoato sódico de butilo; Sodium Butyl Parahydroxybenzoate; Sodium Butylparaben; Натрия бутил Гидроксибензоат.

$C_{11}H_{13}NaO_3$=216.2

CAS — 36457-20-2.

UNII — MAR76J77VS.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Butyl Hydroxybenzoate). A white, odourless or almost odourless, hygroscopic powder. Freely soluble in water and in alcohol. A 0.1% solution in water has a pH of 9.5 to 10.5.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Ethyl Hydroxybenzoate

E215; Ethyl parahydroxybenzoate sodium; Éthyle (parahydroxybenzoate d') sodique; Ethylis Parahydroxybenzoas Natricum; Ethylis parahydroxybenzoas natricus; Ethylparaben sodná sůl; Etilo parahidroksibenzoato natrio druska; Etilparabeno sódico; Etylparahydroxibensoatnatrium; Etyyliparahydroksibentsoaattinatrium; Natriumethyl-4-hydroxybenzoat; Натрия Этил Гидроксибензоат.

$C_9H_9NaO_3$=188.2

CAS — 35285-68-8.

UNII — Z0D00IVA10.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Ethyl Parahydroxybenzoate; Ethyl Hydroxybenzoate Sodium BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in dehydrated alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

The BP 2014 gives Ethylparaben Sodium as an approved synonym.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Methyl Hydroxybenzoate

E219; *p*-Hidroxibenzoato sódico de metilo; Méthyle (parahydroxybenzoate de) sodique; Methylis Parahydroxybenzoas Natricum; Methylis parahydroxybenzoas natricus; Methylparaben Sodium (USAN); Methylparaben sodná sůl; Methylparabenum Natricum; Metilo parahidroksibenzoato natrio druska; Metilparabeno sódico; Metil-parahidroxibenzoátnátrium; Natriummethyl-4-hydroxybenzoat; Natriummetylparahydroxibensoat; Natriummetyylparahydroksibentsoaatti; Parahidroxibenzoato sódico de metilo; Sodium Methyl Parahydroxybenzoate; Sodium Methylparaben; Soluble Methyl Hydroxybenzoate; Натрия Метил Гидроксибензоат.

$C_8H_7NaO_3$=174.1

CAS — 5026-62-0.

UNII — CR6K9C2NHK.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Methyl Parahydroxybenzoate; Sodium Methyl Hydroxybenzoate BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

USNF 31: (Methylparaben Sodium). A white, hygroscopic, powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The incompatibilities and stability of hydroxybenzoates are described under Sodium Propyl Hydroxybenzoate, below.

Sodium Propyl Hydroxybenzoate

E217; *p*-Hidroxibenzoato sódico de propilo; Natriumpropyl-4-hydroxybenzoat; Natriumpropylparahydroxibensoat; Natriumpropyyliparahydroksibentsoaatti; Parahidroxibenzoato sódico de propilo; Propilo parahidroksibenzoato natrio druska; Propilparabeno sódico; Propil-parahidroxibenzoátnátrium; Propyle (parahydroxybenzoate de) sodique; Propylis Parahydroxybenzoas Natricum; Propylis parahydroxybenzoas natricus; Propylparaben Sodium (USAN); Propylparaben sodná sůl; Propylparabenum Natricum; Sodium Propyl Parahydroxybenzoate; Sodium Propylparaben; Soluble Propyl Hydroxybenzoate; Натрия Пропил Гидроксибензоат.

$C_{10}H_{11}NaO_3$=202.2

CAS — 35285-69-9.

UNII — 625NNB0G9N.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sodium Propyl Parahydroxybenzoate; Sodium Propyl Hydroxybenzoate BP 2014). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; practically insoluble in dichloromethane. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

USNF 31: (Propylparaben Sodium). A white, hygroscopic, odourless powder. Freely soluble in water; sparingly soluble in alcohol; insoluble in fixed oils. A 0.1% solution in water has a pH of 9.5 to 10.5. Store in airtight containers.

Incompatibility and stability. The activity of hydroxybenzoates can be adversely affected by the presence of other excipients or active ingredients. There may be adsorption onto substances like magnesium trisilicate, aluminium magnesium silicate, talc, polysorbate 80,[1,2] carmellose sodium,[3] or plastics.[4] Nonionic surfactants can reduce hydroxybenzoate activity,[5] as may essential oils.[6] Other incompatibilities that have been reported include atropine,[7] iron,[4] sorbitol,[8] weak alkalis,[4] and strong acids.[4] Syrup preserved with hydroxybenzoates is incompatible with a range of compounds.[9,10] Methyl hydroxybenzoate 0.1% was reported[11] to be a poor preservative in insulin preparations, especially soluble insulin preparations. Increasing heat or pH can reduce stability and activity;[12] freeze-drying may also lead to a loss of activity.[13]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; 8: 54–6.
2. Allwood MC. The adsorption of esters of p-hydroxybenzoic acid by magnesium trisilicate. *Int J Pharmaceutics* 1982; 11: 101–7.
3. Fawcett JP, *et al.* Binding of parabens to sodium carboxymethylcellulose in oral liquid formulations. *Aust J Hosp Pharm* 1996; 26: 552–4.
4. Haley S. Methylparaben. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2009: 441–5.
5. Yamaguchi M, *et al.* Antimicrobial activity of butylparaben in relation to its solubilization behavior by nonionic surfactants. *J Soc Cosmet Chem* 1982; 33: 297–307.
6. Chemburkar PB, Joslin RS. Effect of flavoring oils on preservative concentrations in oral liquid dosage forms. *J Pharm Sci* 1975; 64: 414–17.
7. Deeks T. Oral atropine sulphate mixtures. *Pharm J* 1983; 230: 481.
8. Runesson B, Gustavii K. Stability of parabens in the presence of polyols. *Acta Pharm Suec* 1986; 23: 151–62.
9. *PSGB Lab Report P/79/2* 1979.
10. *PSGB Lab Report P/80/1* 1980.
11. Allwood MC. The effectiveness of preservatives in insulin injections. *Pharm J* 1982; 229: 340.
12. Sunderland VB, Watts DW. Kinetics of the degradation of methyl, ethyl and n-propyl 4-hydroxybenzoate esters in aqueous solution. *Int J Pharmaceutics* 1984; 19: 1–15.
13. Flora KP, *et al.* The loss of paraben preservatives during freeze drying. *J Pharm Pharmacol* 1980; 32: 577–80.

Uses

The hydroxybenzoate preservatives are alkyl esters of *p*-hydroxybenzoic acid with antibacterial and antifungal properties. They are more active against Gram-positive than against Gram-negative bacteria. They are active over a broad pH range (4 to 8), though are generally more active in acidic solutions. Activity increases with increasing alkyl chain length but aqueous solubility decreases, although this may be overcome by employing the more soluble sodium salts as long as the pH of the preparation is not increased. Activity may also be increased by combining two hydroxybenzoates with short alkyl chains. Another way of increasing activity is to use a hydroxybenzoate with propylene glycol.

Hydroxybenzoates are used as preservatives in pharmaceutical preparations in usual concentrations of up to 0.25%. Methyl hydroxybenzoate and propyl hydroxybenzoate are used together in some preparations. There have been reports of the hydroxybenzoates not being satisfactory preservatives for ophthalmic preparations because of their relative lack of efficacy against some Gram-negative bacteria, particularly *Pseudomonas aeruginosa*. The hydroxybenzoate preservatives are widely used in cosmetics and are also used for food preservation.

Hydroxybenzoates have been used in preparations promoted for the management of skin infections or pruritus.

Adverse Effects and Precautions

Hypersensitivity reactions occur with the hydroxybenzoates. Generally these are of the delayed type, appearing as contact dermatitis. Immediate reactions with urticaria and bronchospasm have occurred rarely.

Breast cancer. Some researchers[1] have questioned whether *p*-hydroxybenzoic acid esters, the most common preservatives found in body care cosmetic products, could increase the incidence of breast cancer in women. The esters have been shown to be oestrogenic *in vitro* and *in vivo* and have been detected in human breast tumour tissue, although a causal association cannot be confirmed.

1. Harvey PW, Darbre P. Endocrine disrupters and human health: could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? *J Appl Toxicol* 2004; 24: 167–76.

Hypersensitivity. Immediate hypersensitivity reactions such as urticaria and bronchospasm with generalised pruritus, have been reported rarely on injection of preparations containing hydroxybenzoates.[1,2] Delayed contact dermatitis occurs more frequently, usually after use of topical medications, but has also occurred after use of an ester or of *p*-hydroxybenzoic acid in oral preparations.[3] Hypersensitivity reactions have also been reported in patients given local anaesthetics containing hydroxybenzoates[1,4] and cross-reactions with other para-amino compounds including benzocaine, paraphenylenediamine, and sulfonamides have occurred rarely.[5]

The incidence of sensitisation to hydroxybenzoates ranges from 0 to 3.5% but has tended to stay relatively constant over time.[5] A report from the North American Contact Dermatitis Group[6] in 1972 provided an incidence of 3%, while another later review[7] of a large number of patients gave an incidence of 2.2%. The Swiss Contact Dermatitis Research Group reported[8] a sensitisation rate of 1.7% based on a one-year study from 1989 to 1990 in 2295 patients.

Subjects with healthy skin exposed to hydroxybenzoates, for example in cosmetics, are considered to have a much lower incidence of reactions than patients with eczema or skin trauma. Unusually, patients who have reacted to a hydroxybenzoate with a contact dermatitis appear to be able to apply that preservative to another unaffected site and yet not suffer a reaction; this has been termed the 'paraben paradox'.[9]

1. Aldrete JA, Johnson DA. Allergy to local anaesthetics. *JAMA* 1969; 207: 356–7.
2. Nagel JE, *et al.* Paraben allergy. *JAMA* 1977; 237: 1594–5.
3. Kaminer Y, *et al.* Delayed hypersensitivity reaction to orally administered methylparaben. *Clin Pharm* 1982; 1: 469–70.
4. Lederman DA, *et al.* An unusual skin reaction following local anesthetic injection: review of the literature and report of four cases. *Oral Surg* 1980; 49: 28–33.
5. Sasseville D. Hypersensitivity to preservatives. *Dermatol Ther* 2004; 17: 251–63.
6. North American Contact Dermatitis Group. Epidemiology of contact dermatitis in North America 1972. *Arch Dermatol* 1973; 108: 537–40.
7. Moore J. Final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. *J Am Coll Toxicol* 1984; 3: 147–209.
8. Perrenoud D, *et al.* Frequency of sensitization to 13 common preservatives in Switzerland. *Contact Dermatitis* 1994; 30: 276–9.
9. Fisher AA. Corticid cream dermatitis and the "paraben paradox". *J Am Acad Dermatol* 1982; 6: 116–7.

Neonates. An *in-vitro* study on serum from neonates with hyperbilirubinaemia indicated that methyl hydroxybenzoate at a concentration of 200 micrograms/mL of serum increased the concentration of free unconjugated bilirubin and interfered with the binding of bilirubin to serum proteins. Methyl hydroxybenzoate was present in an injection of gentamicin sulfate at a concentration of 1.3 to 1.8 mg/mL. Neither gentamicin nor propyl hydroxybenzoate had a significant effect on bilirubin.[1]

1. Loria CJ, *et al.* Effect of antibiotic formulations in serum protein: bilirubin interaction of newborn infants. *J Pediatr* 1976; 89: 479–82.

Pharmacokinetics

Neonates. After intramuscular injection, methyl hydroxybenzoate present in a gentamicin preparation was excreted in the urine of preterm infants to a variable extent and mainly in the conjugated form.[1] *p*-Hydroxybenzoic acid was detected as a metabolite. The injection contained methyl hydroxybenzoate 3.6 mg, propyl hydroxybenzoate 400 micrograms, and gentamicin 80 mg. Propyl hydroxybenzoate was also detected in the urine samples.

1. Hindmarsh KW, *et al.* Urinary excretion of methylparaben and its metabolites in preterm infants. *J Pharm Sci* 1983; 72: 1039–41.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Nisapulvol†; Nisaseptol†; Nisasol†; *Malaysia*: Nisapulvol.

Multi-ingredient Preparations. *Austral.*: Mycoderm; *Hong Kong*: Nisapulvol†; *Malaysia*: Mycoderm†; *Neth.*: Trachitol; *UK*: Brushtox; *USA*: Neosalus; *Venez.*: Glizigen.

Imidurea

Imidazolidinyl Urea; Имидомочевина.

N,N''-Methylenebis[*N'*-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]urea].

$C_{11}H_{16}N_8O_8$=388.3

CAS — 39236-46-9.

UNII — M629807ATL.

Pharmacopoeias. In *USNF*.

USNF 31: (Imidurea). A white odourless powder. Soluble in water and in glycerol; sparingly soluble in propylene glycol; insoluble in most organic solvents. A 1% solution in water has a pH of 6.0 to 7.5. Store in airtight containers.

Profile

Imidurea is used as an antimicrobial preservative in topical pharmaceutical and cosmetic preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Venez.*: Exfoliderm.

Iodoform

Iodoformo; Triyodometano; Yodoformo; Иодоформ.

Tri-iodomethane.

CHI_3=393.7

CAS — 75-47-8.

ATC — D09AA13.

ATC Vet — QD09AA13.

UNII — KX1Z176489.

Pharmacopoeias. In *Jpn* and *US*.

USP 36: (Iodoform). A lustrous greenish-yellow powder or lustrous crystals. It is slightly volatile at ordinary temperatures and distils slowly with steam. It decomposes at high temperatures emitting vapours of iodine. Practically insoluble in water; sparingly soluble in alcohol, in glycerol, and in olive oil; soluble in boiling alcohol; freely soluble in chloroform and in ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Iodoform slowly releases iodine (p. 2336.3) when applied to the tissues and is used for its mild antiseptic action. Bismuth Subnitrate and Iodoform Paste (BPC 1954) (BIPP) has been applied to wounds and abscesses. Sterile gauze impregnated with the paste has also been used for packing cavities after oral and otorhinological surgery.

Adverse effects on the nervous system. Encephalopathy has been associated with the use of bismuth subnitrate and iodoform paste (BIPP) for the packing of wound cavities after ear, nose, and throat, oral, and maxillofacial surgery,[1,2] although there is some debate as to whether the bismuth or the iodoform component is responsible.[1-3] However, encephalopathy has been reported after application of iodoform gauze without bismuth.[4,5] CNS toxicity due to both iodine and bismuth has been reported[6] in an 86-year-old woman from an intra-oral plug of BIPP following partial maxillectomy. Five days after surgery the patient started to experience loss of appetite and lightheadedness, and by day 11 was suffering from fainting episodes, confusion, and paranoid ideation and was becoming increasingly aggressive. On day 14 the BIPP pack was removed; 7 days later the patient's condition improved and when discharged 5 days later she was alert and cooperative.

1. Wilson APR. The dangers of BIPP. *Lancet* 1994; 344: 1313–14.
2. Youngman L, Harris S. BIPP madness: an iatrogenic cause of acute confusion. *Age Ageing* 2004; 33: 406–7.
3. Farrell RWR. Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; 344: 1637–8.
4. Roy P-M, *et al.* Dangers of bismuth iodoform paraffin paste. *Lancet* 1994; 344: 1708.
5. Yamasaki K, *et al.* Delirium and a subclavian abscess. *Lancet* 1997; 350: 1294.
6. Harris RA, Poole A. Beware of bismuth: post maxillectomy delirium. *Aust N Z J Surg* 2002; 72: 846–7.

Hypersensitivity. A retrospective analysis of 185 patients[1] who were treated with a bismuth-iodoform-paraffin paste (BIPP) impregnated ribbon gauze pack after ear surgery found the incidence of allergic reactions to be 5.9%. A fivefold increase risk of developing allergic reactions was also found in those with previous exposure to BIPP. Three cases of allergic contact otitis externa have been reported after the use of bismuth subnitrate and iodoform paste to pack the ear after surgery.[2]

1. Lim PVH, *et al.* Hypersensitive allergic reactions to bismuth-iodoform-paraffin paste following ear surgery. *J Laryngol Otol* 1998; 112: 335–7.
2. Roest MAB, *et al.* Allergic contact otitis externa due to iodoform in BIPP cavity dressings. *Contact Dermatitis* 2002; 46: 360.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Arg.*: Aseptobron; *Austral.*: BIP; *Ital.*: Pasta Iodoformica Radiopaca; *Spain*: Alvogil†; *Switz.*: Alvogyl; *UK*: OxBipp.

Pharmacopoeial Preparations

BPC 1954: Bismuth Subnitrate and Iodoform Paste; Compound Iodoform Paint.

Isopropyl Alcohol

Alkohol izopropylowy; Alcohol isopropílico; Alcohol Isopropylicus; Dimethyl Carbinol; Dimetilcarbinol; Isopropanol; Isopropylalkohol; Isopropylique, alcool; Isopropyylialkoholi; Izopropil Alkol; Izopropil-alkohol; Izopropilo alkoholis; 2-Propanol; Secondary Propyl Alcohol; Изопропиловый Спирт.

Propan-2-ol.

$(CH_3)_2CHOH$=60.10

CAS — 67-63-0.

ATC — D08AX05.

ATC Vet — QD08AX05.

UNII — ND2M416302.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.*, *Jpn*, and *US*.

Ph. Eur. 8: (Isopropyl Alcohol). A clear colourless liquid. Miscible with water and with alcohol. Protect from light.

USP 36: (Isopropyl Alcohol). A transparent, colourless, mobile, volatile, flammable liquid with a characteristic odour. Miscible with water, with alcohol, with chloroform, and with ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Uses and Administration

Isopropyl alcohol is an antiseptic with bactericidal properties similar to those of alcohol (p. 1733.2). It is used for preoperative skin cleansing in concentrations of about 60 to 70%, and is an ingredient of preparations used for disinfection of hands and surfaces. Its marked degreasing properties may limit its usefulness in preparations used repeatedly. It is also used as a solvent, especially in cosmetics, perfumes and pharmaceutical preparations, and as a vehicle for other disinfectant compounds.

Propyl alcohol (p. 1768.1) is also used as an antiseptic.

Adverse Effects, Treatment, and Precautions

Isopropyl alcohol is considered to be more toxic than ethyl alcohol (p. 1733.3), and the symptoms of intoxication appear to be similar, except that isopropyl alcohol has no initial euphoric action and gastritis, haemorrhage, pain, nausea, and vomiting are more prominent. The lethal oral dose is reported to be about 240 mL in adults; however, individuals can vary widely in their susceptibilities and toxic symptoms may be produced by as little as 20 mL. Ketoacidosis and ketonuria commonly occur due to the presence of the major metabolite, acetone, in the

circulation. Inhalation of isopropyl alcohol vapour has been reported to produce coma.

Application of isopropyl alcohol to the skin may cause dryness and irritation; suitable precautions should be taken to prevent absorption through the skin, particularly in infants.

Treatment of adverse effects is as for Alcohol, p. 1734.1.

General references.
1. WHO. 2-Propanol. *Environmental Health Criteria 103*. Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc103.htm (accessed 15/03/06)

Children. Reports of chemical skin burns caused by the topical application of isopropyl alcohol in premature infants.[1,2]

Haemorrhagic gastritis in a 2-year-old febrile child was attributed to topical absorption of isopropyl alcohol that had been used for sponge bathing and followed by wrapping the child tightly in a blanket.[3]

1. Schick JB, Milstein JM. Burn hazard of isopropyl alcohol in the neonate. *Pediatrics* 1981; 68: 587–8.
2. Weintraub Z, Iancu TC. Isopropyl alcohol burns. *Pediatrics* 1982; 69: 506.
3. Dyer S, *et al.* Hemorrhagic gastritis from topical isopropanol exposure. *Ann Pharmacother* 2002; 36: 1733–5.

Rectal absorption. Intoxication and raised serum-creatinine concentrations due to absorption of isopropyl alcohol followed its use as a rectal douche.[1] An 85-year-old woman who accidentally received an isopropyl alcohol enema developed rapid CNS depression, renal failure, and metabolic acidosis. She became comatose within 15 minutes and died 12 hours later after a cardiac arrest. Post-mortem examination showed necrosis of the colon.[2]

1. Barnett JM, *et al.* Intoxication after an isopropyl alcohol enema. *Ann Intern Med* 1990; 113: 638–9.
2. Haviv YS, *et al.* Accidental isopropyl alcohol enema leading to coma and death. *Am J Gastroenterol* 1998; 93: 850–1.

Pharmacokinetics

Isopropyl alcohol is readily absorbed from the gastrointestinal tract but there appears to be little absorption through intact skin. The vapour may be absorbed through the lungs. Isopropyl alcohol is metabolised more slowly than ethyl alcohol and about 15% of an ingested dose is metabolised to acetone.

For reports of rectal absorption of isopropyl alcohol, see above.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Medi-Swab; *Canad.*: Alpet E3; Auro-Dri; Dermorapid†; Duonalc†; Isogel†; Viraguard Antiseptic Hand Spray; Viraguard Antiseptic Hand Wipes; Webcol; Zep E-3†; Zep Instant Hand Sanitizer; *Ger.*: Aktivin; C 20; Dolobene Cool; Septoderm Hande; *Ital.*: Esoform Mani-Cute; *S. Afr.*: Medi-Swab†; *Thai.*: Alcohol Sahakarn; Cohol Sahakarn; *Turk.*: Opak†; *UK*: Alcowipe; Medi-Swab; Sterets; Steriwipe; *USA*: Auro-Dri.

Multi-ingredient Preparations. *Arg.*: Pervinox Jabon; Sincerum Dry; *Austral.*: Aqua Ear; Ear Clear for Swimmers Ear; Septivon; Uni-Solve; *Austria*: Dodesept Gefarbt; Dodesept N†; Dodesept; Isozid-H; Kodan; Marcocid; Mycopol; Octeniderm; Skinsept; Sterillium; *Belg.*: Braunoderm; *Canad.*: Baxedin 2% - 70%; Dexidin; Duonalc-E†; Faces Antiseptic†; Germi Stat Prep; Hibistat†; Loris IV; Solu-IV CHD Alcool; Solu-IV CHG Alcohol†; Soluprep CHD-Alcohol; *Chile*: NP-27; Solarcaine Spray Aerosol; *Cz.*: Promanum N; Softa-Man; *Fin.*: ChloraPrep; Sterillium; *Fr.*: Chloraprep; Clinogel Derma+; Clinogel†; Sterillium; *Ger.*: Autoderm Extra; Bacillol AF; Bacillol Foam; Bacillol plus; Bacillol Tissues; Bacillol Wipes; Bacillol†; Betaseptic; Braunoderm; Cutasept; Dibromol†; Freka-Steril†; HD 410; Helipur H plus N; Incidin; Kodan Tinktur Forte; Mucasept-A; Olbas; Poly-Alkohol†; Promanum N; Rutisept extra; Skinman Soft; Skinsept F; Skinsept G; Softasept N; Spitacid; Sterillium; *Gr.*: Chiro Des; Cutasept; Octeniderm; Sterillium; *Hong Kong*: Baxedin; *Indon.*: Mexochrome†; Spitaderm†; *Irl.*: Biofreeze†; Braunoderm†; ChloraPrep; Hibisol†; Manusept; Sterillium; *Israel*: DryEars; Monorapid†; Skin Des†; Sterets H; *Ital.*: Braunoderm; Citrocil Alcolico†; Citromed; Clorexan; Eso Ferri Plus; Panseptil†; Sekucid†; Spitaderm†; *Neth.*: ChloraPrep; Hibisol; Spitaderm†; Sterillium; *Port.*: Braunoderm†; Promanum†; Softasept; Sterillium; *Singapore*: Desderman; Hibisol; Primasept Med; *Swed.*: Chloraprep; Sterillium; *Switz.*: Betaseptic; Braunoderm; Cutasept; Desamon; Hibital†; Hibitane Teinture†; Jodoplex Teinture†; Kodan forte; Octeniderm; Parapic; Promanum N†; Skinsept; *Softa-Man†*; *Softasept N*; *Thai.*: Chlorsep; *UK*: ChloraPrep; Hibi; Hibisol†; Manusept; Medi-Swab H; Sterets H; Swim-Ear; *USA*: BactoShield; Blue Ice Gel; Chlorascrub; Clindacin ETZ; Clindacin P; Cresylate; Dri/Ear; Ear-Dry; Fungi-Nail; Klout; Lycelle; PledgaClin; Tinver.

Homoeopathic Preparations. *Canad.*: ClearAc Cleanser†.

Pharmacopoeial Preparations
USP 36: Azeotropic Isopropyl Alcohol; Isopropyl Rubbing Alcohol.

Isothiazolinones

Isotiazolinonas; Изотиазолины.

Methylchloroisothiazolinone

Metilcloroisotiazolinona; Метилхлоризотиазолин.
5-Chloro-2-methyl-3(2*H*)-isothiazolone; 5-Chloro-2-methyl-4-isothiazolin-3-one.
CAS — 26172-55-4.
UNII — DEL7T5QRPN.

Methylisothiazolinone

Metilisotiazolinona; Метилизотиазолин.
2-Methyl-3(2*H*)-isothiazolone; 2-Methyl-4-isothiazolin-3-one.
CAS — 2682-20-4.
UNII — 229D0E1QFA.

Profile

A mixture of isothiazolinones consisting of methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) in a ratio of about 3:1 is used as a preservative in industry and in cosmetic and household products. It is effective at very low concentrations against a wide spectrum of Gram-positive and -negative bacteria, yeasts, and fungi. The mixture is often referred to as Kathon CG, one of its proprietary names.

Isothiazolinones may cause contact dermatitis and local irritation.

Hypersensitivity. There have been reports of sensitisation and allergic contact dermatitis arising from the use of isothiazolinones in cosmetics, paints and from industrial exposure.[1-11] The incidence of allergy to methylchloroisothiazolinone and methylisothiazolinone (MCI/MI) is reported be dose-related and ranges from less than 1 to 8.4%.[4,8] A study[6] conducted in 4713 patients at 22 European contact dermatitis clinics over a 12 month period from 1988 to 1989 reported the frequency of positive reactions to 100 ppm MCI/MI to be 3%.

Most hypersensitivity reports are related to use in cosmetics, especially 'leave-on' products such as moisturising creams, while the risk attributed to their use in 'rinse-off' products such as shampoos is considered to be minimal.[4,7] A review[7] of such rinse-off products found that they were even well tolerated in MCI/MI sensitised people. Airborne contact dermatitis has been reported in people exposed to MCI/MI in paints.[9,10] Occupational contact allergy and dermatitis due to MCI/MI have also been reported,[11] and there has been a case report of occupational asthma developing in a worker 5 months after starting work in an isothiazolinone manufacturing plant.[5]

1. Björkner B, *et al.* Contact allergy to the preservative Kathon CG. *Contact Dermatitis* 1986; 14: 85–90.
2. De Groot AC, Bos JD. Preservatives in the European standard series for epicutaneous testing. *Br J Dermatol* 1987; 116: 289–92.
3. Fransway AF. Sensitivity to Kathon CG: findings in 365 consecutive patients. *Contact Dermatitis* 1988; 19: 342–7.
4. De Groot AC, Herzheimer A. Isothiazolinone preservative: cause of a continuing epidemic of cosmetic dermatitis. *Lancet* 1989; i: 314–16.
5. Bourke SJ, *et al.* Occupational asthma in an isothiazolinone manufacturing plant. *Thorax* 1997; 52: 746–8.
6. Menné T, *et al.* Contact sensitization to 5-chloro-2-methyl-4-isothiazolin-3-one and 2-methyl-4-isothiazolin-3-one (MCI/MI): a European multicentre study. *Contact Dermatitis* 1991; 24: 334–41.
7. Fewings J, Menné T. An update of the risk assessment for methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) with focus on rinse-off products. *Contact Dermatitis* 1999; 41: 1–13.
8. Mowad CM. Methylchloro-isothiazolinone revisited. *Am J Contact Dermat* 2000; 11: 115–18.
9. Bohn S, *et al.* Airborne contact dermatitis from methylchloroisothiazolinone in wall paints: abolition of symptoms by chemical allergen inactivation. *Contact Dermatitis* 2000; 42: 196–201.
10. Reinhard E, *et al.* Preservation of products with MCI/MI in Switzerland. *Contact Dermatitis* 2001; 45: 257–64.
11. Isaksson M, *et al.* Occupational contact allergy and dermatitis from methylisothiazolinone after contact with wallcovering glue and after a chemical burn from a biocide. *Dermatitis* 2004; 15: 201–5.

Laurylamine Dipropylenediamine

N-(3-Aminopropyl)-*N*-dodecyl-1,3-propanediamine; *N*-(3-Aminopropyl)-*N*dodecylpropane-1,3-diamine; Dodecylbispropylenetriamine; Dodecyldipropylenetriamine; Laurildipropylenetriamine; *N,N*-Bis(3-aminopropyl)dodecylamine; *N,N*-Bis(3-aminopropyl)laurylamine.
$C_{18}H_{41}N_3$=299.5
CAS — 2372-82-9.
UNII — PCJ630BJUE.

Profile

Laurylamine dipropylenediamine is a polyamine disinfectant used for surface disinfection. Related polyamines such as lauryl 1,3-propyldiamine (*N*-dodecylpropane-1,3,-diamine) have been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ger.*: Almyrol; Hexaquart plus; Korsolex AF; Korsolex Plus; Mikrobac.

Lopobutan *(rINN)*

Lauryloxypropyl-β-aminobutyric Acid; Lopobutano; Lopobutanum; Лопобутан.
(±)-3-[[3-(Dodecyloxy)propyl]amino]butyric acid.
$C_{19}H_{39}NO_3$=329.5
CAS — 6582-30-5.
UNII — L6IE0KAZ8O.

Profile

Lopobutan is a beta aminobutyric acid derivative used as an antiseptic.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Fr.*: Steriane.

Magenta

Aniline Red; Basic Fuchsin; Basic Magenta; CI Basic Violet 14; Colour Index No. 42510; Fuchsine; Fucsina; Fucsina básica; Фуксин.
CAS — 569-61-9 (pararosaniline hydrochloride); 632-99-5 (rosaniline hydrochloride).
UNII — SP5C03819W.

Description. Magenta is a mixture of the hydrochlorides of pararosaniline {4-[(4-aminophenyl)(4-iminocyclohexa-2,5-dien-1-ylidene)-methyl]aniline} and rosaniline {4-[(4-aminophenyl){4-iminocyclohexa-2,5-dien-1-ylidene) methyl]-2-methylaniline}.

Pharmacopoeias. In *US*.

USP 36: (Basic Fuchsin). A mixture of rosaniline and pararosaniline hydrochlorides. It contains the equivalent of not less than 88% of rosaniline hydrochloride ($C_{20}H_{20}ClN_3$ = 337.9), calculated on the dried basis. A dark green powder or greenish glistening crystalline fragments with a bronze-like lustre and not more than a faint odour. Soluble in water, in alcohol, and in amyl alcohol; insoluble in ether.

Profile

Magenta is a triphenylmethane antiseptic dye effective against Gram-positive bacteria and some fungi. Magenta Paint (BPC 1973) (Castellani's Paint) was formerly used in the treatment of superficial dermatophytoses.

Decolorised magenta solution (Schiff reagent) is used as a test for the presence of aldehydes.

Concerns about possible carcinogenicity have restricted the use of magenta.

Carcinogenicity. The handling of magenta was not thought to induce carcinogenesis but its actual manufacture may produce tumours. The IARC has concluded that the manufacturing process of magenta involves exposure to substances that are considered to be definite human carcinogens. Pararosaniline hydrochloride (Basic Red 9), and magenta containing it, are considered possibly carcinogenic to humans.[1] Magenta was also considered to be unsafe for use in food.[2]

1. IARC/WHO. Occupational exposures of hairdressers and barbers and personal use of hair colourants; some hair dyes, cosmetic colourants, industrial dyestuffs and aromatic amines. *IARC monographs on the evaluation of carcinogenic risks to humans volume 57* 1993. Available at: http://monographs.iarc.fr/ENG/Monographs/vol57/volume57.pdf (accessed 23/05/06)
2. FAO/WHO. Specifications for the identity and purity of food additives and their toxicological evaluation: food colours and some antimicrobials and antioxidants: eighth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 309* 1965. Also available at: http://libdoc.who.int/trs/WHO_TRS_309.pdf (accessed 28/08/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Ital.*: Fucsina Fenica.

Pharmacopoeial Preparations
BPC 1973: Magenta Paint;
USP 36: Carbol-Fuchsin Topical Solution.

Magnesium Peroxide

Magnesii Peroxidum; Magnesium Perhydrolum; Magnésium, peroxyde de; Magnesiumperoksid; Magnesiumperoxid; Magnézium-peroxid; Magnio peroksidas; Peroxid hořečnatý; Peróxido de magnesio; Перекись магния.

CAS — 1335-26-8; 14452-57-4.
ATC — A02AA03; A06AD03.
ATC Vet — QA02AA03; QA06AD03.
UNII — XBYYJ0TN96.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Peroxide). A mixture of magnesium peroxide and magnesium oxide. It contains not less than 22% and not more than 28% of MgO_2. A white or slightly yellow, amorphous, light powder. Practically insoluble in water and in alcohol; dissolves in mineral acids. Protect from light.

Profile

Magnesium peroxide is used as an antiseptic. It is also an ingredient of preparations for gastrointestinal disorders.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Ozovit.

Multi-ingredient Preparations. *Ital.*: Carbonesia; Ektogan.

Homoeopathic Preparations. *Chile*: Ikoplex No 10; Ikoplex No 11.

Malachite Green

Aniline Green; China Green; CI Basic Green 4; Colour Index No. 42000; Diamond Green B; Verde de malaquita; Viride Malachitum; Zieleń malachitowa; Малахитовая зелень.
[4-(4-Dimethylaminobenzhydrylidene)cyclohexa-2,5-dienylidene]dimethylammonium chloride.
CAS — 569-64-2.
ATC Vet — QP53AX16.
UNII — 12058M7ORO.

Profile

Malachite green is a triphenylmethane antiseptic dye with actions similar to those of brilliant green (p. 1740.2). It has been used for skin disinfection.

Mecetronium Etilsulfate *(BAN, rINN)*

Etilsulfato de mecetronio; Mecetronii Etilsulfas; Mecetronio, etilsulfato de; Mecetronium Ethylsulfate (USAN); Mecetronium Ethylsulphate; Mécétronium, Étilsulfate de; Мецетрония Этилсульфат.
Ethylhexadecyldimethylammonium ethyl sulphate.
$C_{22}H_{49}NO_4S$=423.7.
CAS — 3006-10-8.
UNII — QM95LPV3CA.

Profile

Mecetronium etilsulfate is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is active against bacteria, including mycobacteria, fungi, and viruses, including hepatitis B virus. It is used in alcoholic solution for disinfection of the skin and hard surfaces.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austria*: Sterillium; *Fin.*: Sterillium; *Fr.*: Sterillium; *Ger.*: Bacillol†; Sterillium; *Gr.*: Sterillium; *Irl.*: Sterillium; *Neth.*: Sterillium; *Port.*: Sterillium; *Swed.*: Sterillium.

Merbromin *(rINN)*

Disodium 2,7-dibromo-4-hydroxymercurifluorescein; Merbromina; Merbromine; Merbrominum; Mercurescéine Sodique; Mercurochrome; Mercurodibromofluorescein; Merkurokrom; Мербромин.
The disodium salt of [2,7-dibromo-9-(2-carboxyphenyl)-6-hydroxy-3-oxo-3*H*-xanthen-5-yl]hydroxymercury.
$C_{20}H_8Br_2HgNa_2O_6$=750.7.
CAS — 129-16-8.
ATC — D08AK04.
ATC Vet — QD08AK04.
UNII — M0T18YH28D.

NOTE. The use of the name Merbromin is limited; in some countries it is a trade-mark.

Pharmacopoeias. In *Fr., It., Jpn,* and *Viet.*

Incompatibility. Merbromin is incompatible with acids, most alkaloidal salts, many local anaesthetics, metals, and sulfides. Activity may be reduced in the presence of organic material.

Uses and Administration

Merbromin is a mercurial antiseptic that has been used for disinfection of skin and wounds.

Adverse Effects and Treatment

As for Mercury, p. 2556.1.

General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; 18: 109–60.

Toxicity. Reports of merbromin toxicity have included contact dermatitis[1] and epidermal cell toxicity.[2] A fatality has occurred after transcutaneous absorption of merbromin during treatment of infected omphalocele (umbilical hernia)[3,4] and death due to shock, with aplastic anaemia, has followed application to surgical wounds and decubitus areas.[5] Anaphylaxis has also occurred.[6] Extensive absorption after ingestion has also been reported.[7] There has also been a case report[8] of severe encephalopathy and meningitis within 24 hours of an accidental intrathecal application into a CSF fistula.

1. Camarasa G. Contact dermatitis from mercurochrome. *Contact Dermatitis* 1976; 2: 120.
2. Anonymous. Topical antiseptics and antibiotics. *Med Lett Drugs Ther* 1977; 19: 83–4.
3. Yeh T-P, *et al.* Mercury poisoning from mercurochrome therapy of infected omphalocele. *Lancet* 1978; i: 210.
4. Yeh TP, *et al.* Mercury poisoning from mercurochrome therapy of an infected omphalocele. *Clin Toxicol* 1978; 13: 463–7.
5. Slee PHTJ, *et al.* A case of Merbromin (mercurochrome) intoxication possibly resulting in aplastic anemia. *Acta Med Scand* 1979; 205: 463–6.
6. Galindo PA, *et al.* Mercurochrome allergy: immediate and delayed hypersensitivity. *Allergy* 1997; 52: 1138–41.
7. Magarey JA. Absorption of mercurochrome. *Lancet* 1993; 342: 1424.
8. Stark AM, *et al.* Accidental intrathecal mercury application. *Eur Spine J* 2004; 13: 241–3.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Medichrom; *Fr.*: Solucrom†; *Gr.*: Merbromin; Mercurochrome; *S.Afr.*: Red Seal†; *Spain*: Cinfacromin†; Mercromina; Mercurin†; Mercurobromo†; Mercutina Brota†; *Turk.*: Mersisol; Mersol.

Multi-ingredient Preparations. *S.Afr.*: Achromide; Daromide†; Ung Vermleigh.

Mercurobutol *(rINN)*

L-542; Mercurobutolum; Меркуробутол.
4-*tert*-Butyl-2-chloro-mercuriphenol.
$C_{10}H_{13}ClHgO$=385.3.
CAS — 498-73-7.
UNII — 8HJ49MW6V4.

Pharmacopoeias. In *Fr.*

Profile

Mercurobutol is an organic mercurial antiseptic with antifungal properties. It has been used in the treatment of infections of the skin and mucous membranes.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Gr.*: Sabenyl.

Metalkonium Chloride *(rINN)*

Cloruro de metalconio; Dodecarbonium Chloride; Metalconio, cloruro de; Metalkonii Chloridum; Métalkonium, Chlorure de; Металкония Хлорид.
Benzyl(dodecylcarbamoylmethyl)dimethylammonium chloride.
$C_{23}H_{41}ClN_2O$=397.0.
CAS — 100-95-8.
UNII — IM6BZ8F57J.

Profile

Metalkonium chloride is an antiseptic used for skin disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ital.*: Theotex.

Methylated Spirits

Alcoholes desnaturalizados; Денатурированный Спирт(denatured alcohol).
CAS — 8013-52-3 (ethyl alcohol-methyl alcohol mixture, industrial methylated spirit).

Description. Three classes of methylated spirits are listed under the Methylated Spirits Regulations, 1987 (SI 1987 No. 2009): industrial methylated spirits, mineralised methylated spirits, and denatured ethanol (denatured alcohol).

Industrial Methylated Spirits is defined as 95 parts by volume of spirits mixed with wood naphtha (mostly methyl alcohol—p. 2196.2) 5 parts by volume. **Mineralised methylated spirits** is spirits mixed with wood naphtha 9.5 parts by volume and crude pyridine 0.5 parts by volume, and to every 2000 litres of this mixture is added 7.5 litres of mineral naphtha (petroleum oil) and 3 g of synthetic organic dyestuff (methyl violet). This is the only variety that may be sold in Great Britain for general use. **Denatured ethanol** is 999 parts by volume of spirits (of a strength not less than 85%) mixed with 1 part by volume of tertiary butyl alcohol, and to this mixture is added Bitrex (denatonium benzoate) 10 mg/litre.

As Industrial Methylated Spirit may contain small amounts of acetone it should not be used for the preparation of iodine solutions, since an irritating compound is formed by reaction between iodine and acetone; for such preparations Industrial Methylated Spirit (Ketone-free) should be used.

Pharmacopoeias. *Br.* includes Industrial Methylated Spirit and Industrial Methylated Spirit (Ketone-free).

BP 2014: (Industrial Methylated Spirit). A mixture of 19 volumes of ethyl alcohol of an appropriate strength with 1 volume of approved wood naphtha. Two strengths are available containing 99% and 95% v/v alcohol (also known as 74 OP and 66 OP respectively). It is a colourless, clear, mobile, volatile liquid with an odour which is spirituous and of wood naphtha. B.p. is about 78 degrees.

The BP 2014 gives Industrial Methylated Spirits and IMS as approved synonyms.

BP 2014: (Industrial Methylated Spirit (Ketone-free)). A mixture of the same strength as Industrial Methylated Spirit, but it is substantially free from ketones, containing not more than the equivalent of 500 ppm of acetone.

Uses and Administration

Industrial methylated spirit, in a concentration of about 70%, is the usual form in which alcohol (p. 1733.1) is used for disinfection. It is applied externally for its astringent action, but mucous membranes and excoriated skin surfaces must be protected. It may be used for skin preparation before injection.

Methylated spirits may be used in the form of Surgical Spirit (BP 2014), a mixture of methyl salicylate (0.5% v/v), diethyl phthalate (2% v/v), and castor oil (2.5% v/v) in industrial methylated spirit.

Adverse Effects

As for Alcohol, p. 1733.3, and Methyl Alcohol, p. 2196.2. Adverse effects are due chiefly to consumption of methylated spirits rather than its topical use as a disinfectant.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Irl.*: Skinman; *Ital.*: Bsosan Gel.

Pharmacopoeial Preparations
BP 2014: Surgical Spirit.

Methylbenzethonium Chloride *(BAN, rINN)*

Cloruro de metilbencetonio; Methylbenzethonii Chloridum; Méthylbenzéthonium, Chlorure de; Metilbencetonio, cloruro de; Метилбензетония Хлорид.
Benzyldimethyl-2-[2-[4-(1,1,3,3-tetramethylbutyl)-o-tolyloxy]ethoxy]ethylammonium chloride monohydrate.
$C_{28}H_{44}ClNO_2.H_2O$=480.1.
CAS — 25155-18-4 (anhydrous methylbenzethonium chloride); 1320-44-1 (methylbenzethonium chloride monohydrate).
UNII — 4XKK0M5H9M (anhydrous methylbenzethonium chloride); WOA57K8S5V (methylbenzethonium chloride monohydrate).

Pharmacopoeias. In *US.*

USP 36: (Methylbenzethonium Chloride). White hygroscopic crystals with a mild odour. Soluble 1 in 0.8 of water, 1 in 0.9 of alcohol, 1 in more than 10 000 of chloroform, and 1

in 0.7 of ether. Solutions are neutral or slightly alkaline to litmus. Store in airtight containers.

Profile

Methylbenzethonium chloride is a quaternary ammonium disinfectant and antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used topically for minor infections or irritation of the skin.

Leishmaniasis. Topical treatment of cutaneous leishmaniasis (p. 922.1) with methylbenzethonium chloride 12% and paromomycin sulfate has proved beneficial.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Israel*: Leshcutan; *USA*: Acnotex; Dermasept Antifungal; Drytex; Finac; Oraseptt.

Pharmacopoeial Preparations
USP 36: Methylbenzethonium Chloride Lotion; Methylbenzethonium Chloride Ointment; Methylbenzethonium Chloride Topical Powder.

Methylrosanilinium Chloride *(BAN, rINN)*

CI Basic Violet 3; Cloruro de metilrosanilina; Colour Index No. 42555; Crystal Violet; Fiolet krystaliczny; Gentian Violet; Hexamethylpararosaniline Chloride; Jansiyen Moru; Kristal Viyole; Kristallviolett; Methylrosaniline Chloride; Methylrosanilinii Chloridum; Méthylrosanilinium, Chlorure de; Methylrosanilinium-chlorid; Methylrosaniliniumchlorid; Metilrosanilina, cloruro de; Metilrozanilinio chloridas; Metilrozanilinyum Klorür; Metylrosaniliniumklorid; Metyylirosaniliniumkloridi; Pyoctaninum Caeruleum; Viola Crystallina; Метилрозанилиния Хлорид.
4-[4,4'Bis(dimethylamino)benzhydrylidene]cyclohexa-2,5-dien-1-ylidenedimethylammonium chloride.
$C_{25}H_{30}ClN_3$=408.0
CAS — 548-62-9.
ATC — D01AE02; G01AX09.
ATC Vet — QD01AE02; QG01AX09.
UNII — J4Z741D6O5.

NOTE. The name methyl violet—CI Basic Violet 1; Colour Index No. 42535—has been used as a synonym for methylrosanilinium chloride, but is applied to a mixture of the hydrochlorides of the higher methylated pararosanilines consisting mainly of the tetramethyl-, pentamethyl-, and hexamethyl-compounds.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, and *US*.

Jpn includes a mixture of hexamethylpararosaniline hydrochloride with the tetramethyl- and pentamethyl-compounds.

Ph. Eur. 8: (Methylrosanilinium Chloride). A dark green, hygroscopic, shiny powder. It contains not more than 10% of pentamethyl-*p*-rosanilinium chloride. It is also known as crystal violet and gentian violet. Sparingly soluble in water; freely soluble in alcohol and in dichloromethane. Store in airtight containers.

USP 36: (Gentian Violet). A dark green powder or greenish, glistening pieces with a metallic lustre, and with not more than a faint odour. Sparingly soluble in water; soluble 1 in 10 of alcohol and 1 in 15 of glycerol; soluble in chloroform; insoluble in ether.

Incompatibility. The antimicrobial activity of methylrosanilinium chloride may be reduced through incompatibilities, decreasing pH, or through combination with organic matter.

The antibacterial activity of methylrosanilinium chloride was inhibited in suspensions of bentonite with which it formed a stable complex.[1]

1. Harris WA. The inactivation of cationic antiseptics by bentonite suspensions. *Australas J Pharm* 1961; 42: 583–8.

Uses and Administration

Methylrosanilinium chloride is a triphenylmethane antiseptic dye effective against some Gram-positive bacteria, particularly *Staphylococcus* spp., and some pathogenic fungi such as *Candida* spp. It is much less active against Gram-negative bacteria and ineffective against acid-fast bacteria and bacterial spores. Its activity increases as pH increases.

Methylrosanilinium chloride has been applied topically as a 0.25 to 2.0% aqueous solution or as a cream for the treatment of bacterial and fungal infections, but in the UK its use is now restricted to application to unbroken skin because of concern over *animal* carcinogenicity. It has also been used as a 0.5% solution with brilliant green 0.5% (Bonney's blue) for skin marking before surgery.

Adverse Effects and Precautions

Topical application of methylrosanilinium chloride can produce irritation and ulceration of mucous membranes. Ingestion of methylrosanilinium chloride during prolonged or frequent treatment for oral candidiasis has resulted in oesophagitis, laryngitis, and tracheitis; ingestion may also cause nausea, vomiting, diarrhoea, and abdominal pain. In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds. Contact with the eyes or broken skin should be avoided. Methylrosanilinium chloride may stain skin and clothing.

Animal carcinogenicity has restricted its use.

Carcinogenicity. Methylrosanilinium chloride has been shown *in vitro* to be capable of interacting with DNA of living cells,[1] and has demonstrable carcinogenicity in *mice*.[2]

1. Rosenkranz HS, Carr HS. Possible hazard in use of gentian violet. *BMJ* 1971; 3: 702–3.
2. MAFF Food Advisory Committee. Final report on the review of the Colouring Matter in Food Regulations 1973: FdAC/REP/4. London: HMSO, 1987.

Effects on the skin and mucous membranes. Necrotic skin reactions have been reported after the use of topical 1% aqueous solutions of methylrosanilinium chloride;[1] areas affected include the submammary folds, gluteal fold, genitalia, and toe-webs. Similar reactions were seen in 2 patients after use of 1% methylrosanilinium chloride or brilliant green on stripped skin.[1] Oral ulceration developed in all of 6 neonates treated with aqueous methylrosanilinium chloride 0.5 or 1% for oral candidiasis.[2]

In the UK it is recommended that methylrosanilinium chloride should not be applied to mucous membranes or open wounds.

1. Björnberg A, Mobacken H. Necrotic skin reactions caused by 1% gentian violet and brilliant green. *Acta Derm Venereol (Stockh)* 1972; 52: 55–60.
2. Horsfield P, *et al.* Oral irritation with gentian violet. *BMJ* 1976; 2: 529.

Effects on the urinary tract. Severe haemorrhagic cystitis rapidly occurred in a 32-year-old woman after accidental injection through the urethra of a solution of methylrosanilinium chloride 1% and alcohol 2%.[1] Two cases of severe cystitis were also reported after instillation into the bladder of an undiluted solution containing methylrosanilinium chloride and brilliant green 1:1 (Bonney's blue).[2] Haemorrhagic cystitis has also been reported in a 16-month-old boy after a diluted solution of methylrosanilinium chloride 1% was instilled into his bladder during an inguinal herniorrhaphy.[3]

1. Walsh C, Walsh A. Haemorrhagic cystitis due to gentian violet. *BMJ* 1986; 293: 732.
2. Christmas TJ, *et al.* Bonney's blue. *Lancet* 1988; ii: 459–60.
3. Kim SJ, *et al.* Hemorrhagic cystitis due to intravesical instillation of gentian violet completely recovered with conservative therapy. *Yonsei Med J* 2003; 44: 163–5.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Pol.*: Pioktanina; *Spain*: Vigencial; *Thai.*: Pyrad-Violet; *Turk.*: Viojen.

Multi-ingredient Preparations. *Chile*: Faxet.

Pharmacopoeial Preparations
USP 36: Gentian Violet Cream; Gentian Violet Topical Solution.

Miramistin

Myramistin; Мирамистин.
Alkylamidopropylmethylbenzylammonium chloride.
$C_{26}H_{47}N_2OCl$=439.1
CAS — 126338-77-0; 15809-19-5.

Profile

Miramistin is a quaternary ammonium antiseptic used for disinfection of the skin and mucous membranes. It is also included in topical preparations for skin disorders when prone to infection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Rus.*: Okomistin (Окомистин); *Ukr.*: Myramydez (Мирамидез); Oftamirin (Офтамирин).

Multi-ingredient Preparations. *Ukr.*: Panthestin (Пантестин); Trimistin (Тримистин).

Miripirium Chloride *(rINN)*

Cloruro de miripirio; Miripirii Chloridum; Miripirio, cloruro de; Miripirium, Chlorure de; Myristyl-gamma-picolinium Chloride; Мирипирия Хлорид.
4-Methyl-1-tetradecylpyridinium chloride.
$C_{20}H_{36}ClN$=326.0
CAS — 7631-49-4 (miripirium); 2748-88-1 (miripirium chloride).
UNII — 3D6CWI0P23.

Profile

Miripirium chloride is used as an antimicrobial preservative in some pharmaceutical products.

Hypersensitivity. Two patients who had a delayed hypersensitivity reaction to retrobulbar injection of methylprednisolone acetate suspension (*Depo-Medrol*)[1] were found on intradermal testing to be sensitive to methylprednisolone and to the preservative miripirium chloride included in the formulation. A similar case of contact allergy has been reported[2] in a 56-year-old woman who received an intra-articular injection of methylprednisolone acetate. Patch testing showed allergy to the preservative miripirium chloride.

1. Mathias CGT, Robertson DB. Delayed hypersensitivity to a corticosteroid suspension containing methylprednisolone. *Arch Dermatol* 1985; 121: 258–61.
2. Färm G, Eriksson I. Contact allergy to miripirium chloride in Depo-Medrol. *Contact Dermatitis* 2001; 44: 127.

Miristalkonium Chloride *(BAN, rINN)*

Cloruro de miristalconio; Miristalconio, cloruro de; Miristalkonii Chloridum; Miristalkonium, Chlorure de; Myristylbenzalkonium Chloride; Tetradecylbenzyldimethylammonium Chloride; Миристалкония Хлорид.
Benzyldimethyltetradecylammonium chloride.
$C_{23}H_{42}ClN$=368.0
CAS — 139-08-2.
ATC — R02AA10.
ATC Vet — QR02AA10.
UNII — 0W255OL75T.

Profile

Miristalkonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It has been used in creams and lotions for disinfection of the skin and has been an ingredient of sprays used for the treatment of minor infections of the mouth and throat. It is also used as a vaginal spermicide.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Alpagelle.

Multi-ingredient Preparations. *Fr.*: Sterlane; *Ital.*: Eburdent F.

Monothioglycerol

α-Monothioglycerol; Monothioglicerol; Thioglycerol; Тиоглицерин.
3-Mercaptopropane-1,2-diol.
$C_3H_8O_2S$=108.2
CAS — 96-27-5.
UNII — AAQ1P0WSXJ.

Pharmacopoeias. In *USNF*.

USNF 31: (Monothioglycerol). A colourless or pale yellow, viscous, hygroscopic liquid with a slight odour of sulfide. Freely soluble in water; miscible with alcohol; insoluble in ether. A 10% solution in water has a pH of 3.5 to 7.0. Store in airtight containers.

Profile

Monothioglycerol is used as an antoxidant preservative in pharmaceutical preparations. It has some antimicrobial activity.

Nitromersol

Нитромерсол.
5-Methyl-2-nitro-7-oxa-8-mercurabicyclo[4.2.0]octa-1,3,5-triene.
$C_7H_5HgNO_3$=351.7
CAS — 133-58-4.
UNII — RU6242GP15.

Pharmacopoeias. In *US*.

USP 36: (Nitromersol). A brownish-yellow to yellow odourless powder or granules. Very slightly soluble in water, in alcohol, in acetone, and in ether; soluble in solutions of alkalis and of ammonia with the formation of salts. Store in airtight containers. Protect from light.

The symbol † denotes a preparation no longer actively marketed

Incompatibility. Nitromersol is incompatible with metals and sulfides. Its antimicrobial activity may be diminished in the presence of organic material.

Uses and Administration

Nitromersol is a mercurial antiseptic effective against some bacteria. It is not effective against spores or acid-fast bacteria. It has been used for superficial skin infections and for disinfection of the skin before surgical treatment.

Adverse Effects and Treatment

As for Mercury, p. 2556.1.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Chile*: Butesin†.

Pharmacopoeial Preparations
USP 36: Nitromersol Topical Solution.

Nordihydroguaiaretic Acid

Acidum Nordihydroguaiareticum; NDGA; Nordihidroguayarético, ácido; Nordihydroguajareettiha ppo; Nordihydroguajaretsyra; Нордигидроваяреговая Кислота.
4,4'-(2,3-Dimethyltetramethylene)bis(benzene-1,2-diol).
$C_{18}H_{22}O_4$=302.4
CAS — 500-38-9.

Profile

Nordihydroguaiaretic acid has been used as an antoxidant preservative. Allergic contact dermatitis has been reported.

Noxytiolin *(BAN, rINN)*

Noxitiolina; Noxythiolin; Noxytioline; Noxytiolinum; Нокситиолин.
1-Hydroxymethyl-3-methyl-2-thiourea.
$C_3H_8N_2OS$=120.2
CAS — 15599-39-0.
ATC — B05CA07.
ATC Vet — QB05CA07.
UNII — 4DN3AF1FU6.

Uses and Administration

Noxytiolin is an antiseptic with wide antibacterial and antifungal actions. It may act by slowly releasing formaldehyde in solution.

For instillation into, or irrigation of, the peritoneal cavity or other body cavities, a 1 or 2.5% solution is used. Solutions of noxytiolin should be warmed to 37 degrees before instillation or irrigation. Treatment is usually for 3 to 7 days. The normal total daily amount used in adults should not exceed 5 g for instillation or 10 g for continuous irrigation.

Action. Although noxytiolin has generally been thought to act, at least in part, by slowly releasing formaldehyde into solution, it has been reported[1] that much smaller amounts are released than have previously been thought and that the antimicrobial effects of noxytiolin solutions cannot be attributed solely to the presence of formaldehyde. There is evidence *in vitro* that noxytiolin might reduce the adherence of micro-organisms to epithelial surfaces.[2]

1. Gorman SP, *et al.* Formaldehyde release from noxythiolin solutions. *Pharm J* 1984; 234: 62–3.
2. Anderson L, *et al.* Clinical implications of the microbial anti-adherence properties of noxythiolin. *J Pharm Pharmacol* 1985; 37 (suppl): 64P.

Infections of the pleural cavity. Three patients with pleural empyema or pneumonectomy space infection were treated by irrigation of the cavity with noxytiolin 1% in normal saline for 3 hours, followed by drainage for 1 hour, the cycle being repeated 4-hourly. Infection was eradicated within 21 days in all 3 patients.[1]

1. Rosenfeldt FL, *et al.* Comparison between irrigation and conventional treatment for empyema and pneumonectomy space infection. *Thorax* 1981; 36: 272–7.

Adverse Effects and Treatment

When noxytiolin is given initially by irrigation for the treatment of the purulent infected bladder there may be an intense reaction with a burning sensation and the passage of large fibrin clumps. Giving it with a local anaesthetic such as tetracaine hydrochloride may control the pain.

Breath odour. A pervasive sweet breath odour characteristic of decaying vegetables has been noted in patients treated with peritoneal dialysis fluid containing noxytiolin.[1] The odour was attributed to unidentified sulfur metabolites.

1. Stewart WK, Fleming LW. Use your nose. *Lancet* 1983; i: 426.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Noxyflex†; *Irl.*: Noxyflex S†; *UK*: Noxyflex S.

Octafonium Chloride *(BAN, rINN)*

Cloruro de octafonio; Octafonii Chloridum; Octafonio, cloruro de; Octafonium, Chlorure d'; Octaphonium Chloride; Phenoctide; Октафония Хлорид.
Benzyldiethyl-2-[4-(1,1,3,3-tetramethylbutyl)phenoxy]ethylammonium chloride monohydrate.
$C_{27}H_{42}ClNO_2H_2O$=450.1
CAS — 15687-40-8 (anhydrous octafonium chloride); 78-05-7 (anhydrous octafonium chloride).
UNII — 5SEY06I0DA.

Profile

Octafonium chloride is a quaternary ammonium antiseptic with actions and uses similar to those of other cationic surfactants (see Cetrimide, p. 1742.1). It is used in topical preparations for skin disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Irl.*: Germolene; *S.Afr.*: Germolene†; *UK*: Germolene.

Octenidine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de octenidina; Octenidina, hidrocloruro de; Octénidine, Chlorhydrate d'; Octenidini Hydrochloridum; Win-41464-2 (octenidine hydrochloride); Win-41464-6 (octenidine saccharin); Win-41464 (octenidine); Октенидина Гидрохлорид.
1,1',4,4'-Tetrahydro-*N*,*N*'-dioctyl-1,1'-decamethylenedi-(4-pyridylideneamine) dihydrochloride.
$C_{36}H_{62}N_4.2HCl$=623.8
CAS — 71251-02-0 (octenidine); 70775-75-6 (octenidine hydrochloride).
UNII — U84956NU4B.

Profile

Octenidine is a bispyridine bactericidal antiseptic with some antiviral and antifungal activity. It has been used as the hydrochloride for skin and mucous membrane disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Switz.*: Stellisan.

Multi-ingredient Preparations. *Austria*: Octeniderm; Octenisept; *Cz.*: Octenisept; *Ger.*: Linola Wundgel; Octenisept; *Gr.*: Octeniderm; Octenisept; *Pol.*: Octenisept; *Rus.*: Octenisept (Октенисепт); *Singapore*: Octenisan; Octenisept Wound Gel; Octenisept; *Switz.*: Octeniderm; Octenisept; *Ukr.*: Octenisept (Октенисепт); Oktenisept (Октенисепт).

Octyldecyldimethylammonium Chloride

Decyldimethyloctylammonium Chloride; Decyloctyldimethylammonium Chloride; Octyl Decyl Dimethyl Ammonium Chloride; Quaternium-24; Октилдецилдиметиламмоний Хлорид.
N,*N*-Dimethyl-*N*-octyl-1-decanaminium chloride.
$C_{20}H_{44}ClN$=334.0
CAS — 32426-11-2.
UNII — 0T2NG1539G.

Profile

Octyldecyldimethylammonium chloride is a quaternary ammonium disinfectant used in preparations for disinfection of hard surfaces and the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *USA*: Vi Rid-Ready.

Orthophenylphenol

2-Biphenylol; E231; E232 (sodium-o-phenylphenol); 2-Hydroxybiphenyl; o-Hydroxydiphenyl; Ortofenilfenol; Ортофенилфенол.
(1,1'-Biphenyl)-2-ol.
$C_{12}H_{10}O$=170.2
CAS — 90-43-7.
ATC — D08AE06.
ATC Vet — QD08AE06.
UNII — D343Z75HT8.

Profile

Orthophenylphenol is a phenolic disinfectant with antimicrobial properties similar to those of chloroxylenol (p. 1748.2). It is used for disinfection of skin, hands, instruments, and hard surfaces. It also has many industrial and agricultural uses as a preservative for a wide range of materials, particularly against moulds and rots. Sodium-*o*-phenylphenol has been used similarly.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Amocid; *Ital.*: Citromedics Disinfettante; Citrosteril Aspiratori; Crescom; Esofenol 60; Germozero; Helix I; Higesan: Neo Esoformolo.

Multi-ingredient Preparations. *Austria*: Dodesept Gefarbt; Dodesept; Kodan; *Canad.*: Aseptone 1; Aseptone 2; Aseptone 5; *Ger.*: Bomix†; Freka-Derm†; Freka-Sept 80†; Helipur; Kodan Tinktur Forte; *Ital.*: Esofenol Ferri; Germozero Dermo; Helipur; Hygienist; Norica Plus; Sangen Casa; Sterosan; *Singapore*: Desderman; Primasept Med; *Switz.*: Kodan forte; *UK*: Eradicil; *USA*: BTK-Plus†.

Oxychlorosene *(USAN)*

Monoxychlorosene; Oxicloroseno; Оксихлорозен.
$C_{20}H_{34}O_3S$,HOCl=407.0
CAS — 8031-14-9.
UNII — 3214M86B2N.

Oxychlorosene Sodium *(USAN)*

Oxicloroseno sódico; Sodium Oxychlorosene; Оксихлорозен Натрий.
CAS — 52906-84-0.
UNII — N693Q6RADF.

Profile

Oxychlorosene is the hypochlorous acid complex of a mixture of the phenyl sulfonate derivatives of aliphatic hydrocarbons. It is a chlorine-releasing antiseptic with the general properties of chlorine, p. 1746.2.

A 0.4% solution of oxychlorosene sodium has been used for cleansing wounds (although chlorine-releasing antiseptics are generally regarded as too irritant for this purpose—see Disinfection, Wounds, under Uses and Administration of Sodium Hypochlorite, p. 1769.1) and for pre-operative skin preparation; a 0.1 or 0.2% solution has been used in urological and ophthalmological disinfection.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *USA*: Clorpactin WCS-90.

Oxymethurea

Carbamol; Dihydroxymethyl Carbamide; Dimethylolurea; Oximeturea; Диметилолмочевина; *N*,*N*'-di(hydroksimetyyli) karbamidi; *N*,*N*'-di(hydroximetyl)-karbamid; *N*,*N*'-di(hydroxymethyl)carbamidum.
N,*N*'-Bis(hydroxymethyl)urea.
$C_3H_8N_2O_3$=120.1
CAS — 140-95-4.
UNII — N68H97CAWG.

Profile

Oxymethurea is an antiseptic included in multi-ingredient preparations intended for the topical treatment of ear infections.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India*: Otogesic.

Parachlorophenol

Paraclorofenol; Парахлорофенол.
4-Chlorophenol.
C_6H_5ClO=128.6
CAS — 106-48-9.
UNII — 3DLC36A01X.

Pharmacopoeias. In *US*.

US also includes camphorated parachlorophenol.

USP 36: (Parachlorophenol). It consists of white or pink crystals with a characteristic phenolic odour. M.p. about 42 degrees; congealing temperature between 42 degrees and 44 degrees. Sparingly soluble in water and in liquid paraffin; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble in soft paraffin. A 1% solution in water is acid to litmus. Store in airtight containers. Protect from light.

USP 36: (Camphorated Parachlorophenol). It contains not less than 33% and not more than 37% of parachlorophenol and not less than 63% and not more than 67% of camphor, with the sum of the percentages of parachlorophenol and camphor not less than 97% and not more than 103%. Store in airtight containers. Protect from light.

Profile

Parachlorophenol is a chlorinated phenolic disinfectant and antiseptic with similar properties to phenol (below). Camphorated parachlorophenol has been used in dentistry in the treatment of infected root canals.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Canad.*: Cresophene; *Fr.*: Cidapex†; Endotine; Mepacyl; *Ital.*: Esofenol Ferri; Pasta Iodoformica Radiopaca; *Spain*: Cresophene.

Paraformaldehyde

Paraform; Paraformaldehído; Paraformic Aldehyde; Paraformol; Polymerised Formaldehyde; Polyoxymethylene; Параформальдегид.
$(CH_2O)_n$
CAS — 30525-89-4.
UNII — Y19UC83H8E.

Pharmacopoeias. In *Jpn*.

Uses and Administration

Paraformaldehyde is a disinfectant and antiseptic with the properties and uses of formaldehyde (p. 1752.2) and is used as a source of formaldehyde. To disinfect rooms it has been vapourised by heating. Tablets prepared for this purpose should be coloured by the addition of a suitable blue dye.

Paraformaldehyde has been used in lozenges for the treatment of minor throat infections. In dentistry, it has been used as an obtundent for sensitive dentine and as an antiseptic in mummifying pastes and for root canals. Paraformaldehyde may also be used for the decontamination of equipment thought to be contaminated with the spores of *Bacillus anthracis*.

Adverse Effects, Treatment, and Precautions

As for Formaldehyde Solution, p. 1752.3. There have been reports of allergic reactions and nerve damage associated with the dental use of paraformaldehyde as a root canal sealant; it should not extrude beyond the apex.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Israel*: Formalin; *Ital.*: Esoform 7 mc; Esoform 70 mc.

Multi-ingredient Preparations. *Canad.*: Endomethasone; *Fr.*: Caustinerf sans Arsenic; Yranicid sans Arsenic; *Gr.*: Endomethasone†; *Ital.*: Eso 70; Pasta Devitalizzante.

Peracetic Acid

Acetyl Hydroperoxide; Ácido peroxiacético; Acidum Peraceticum; Kyselina peroctová; Peracético, ácido; Peroxyacetic Acid; Надуксусная Кислота; Перуксусная Кислота.
$C_2H_4O_3$=76.05.
CAS — 79-21-0.
UNII — I6KPI2E1HD.

Uses

Peracetic acid is a strong oxidising disinfectant. It is active against many micro-organisms including bacteria, spores, fungi, and viruses. It is used for disinfecting medical equipment including dialysers and endoscopes. It is used in the food industry and for disinfecting sewage sludge, and has been used as a spray for sterilisation of laboratories.

Reviews.
1. Kitis M. Disinfection of wastewater with peracetic acid: a review. *Environ Int* 2004; **30**: 47–55.

Disinfection of dialysis equipment. For use of peracetic acid with hydrogen peroxide in the disinfection of dialysis equipment, see under Hydrogen Peroxide, p. 1756.1.

Disinfection of endoscopes. Peracetic acid has been used to disinfect endoscopes;[1,2] it is a possible alternative to glutaral (see p. 1731.2).
1. Bradley CR, *et al.* Evaluation of the Steris system 1 peracetic acid endoscope processor. *J Hosp Infect* 1995; **29**: 143–51.
2. Middleton AM, *et al.* Disinfection of bronchoscopes, contaminated in vitro with Mycobacterium tuberculosis, Mycobacterium avium-intracellulare and Mycobacterium chelonae in sputum, using stabilized, buffered peracetic acid solution ('Nu-Cidex'). *J Hosp Infect* 1997; **37**: 137–43.

Adverse Effects and Precautions

Concentrated peracetic acid is corrosive to the skin. Inhalation may produce respiratory symptoms, including pulmonary oedema, although commercial solutions are claimed to have low vapour activity.

Occupational exposure. Although corrosive and highly irritating to skin, eyes, mucous membranes and respiratory tract, solutions of peracetic acid (with hydrogen peroxide) were thought unlikely to cause sensitisation leading to hypersensitivity reactions in healthcare workers who were occupationally exposed. In contrast, *o*-phthaldialdehyde, although its sensitising potential was much lower than that of glutaral, might cause respiratory and dermal sensitisation.[1]
1. Rideout K, *et al.* Considering risks to healthcare workers from glutaraldehyde alternatives in high-level disinfection. *J Hosp Infect* 2005; **59**: 4–11.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Sekusept; *Ital.*: Esocetic; Esodrox; Ferrister†; Renaxid†; SaniDrox; Sekusept; Sporidox Plus†; *Singapore*: PeraSafe.

Multi-ingredient Preparations. *Canad.*: Actril; *Fr.*: Anioxyde†; *Ger.*: AdaptaCide PAA-C; *Ital.*: Adasport†; Peresal†; *Singapore*: Virkon.

Phenethyl Alcohol *(BANM)*

Alcohol feniletílico; Alcohol Phenylethylicus; Alkohol fenyloetylowy; Benzyl Carbinol; Phenethanolum; Phenylethyl alcohol; Фенетиловый Спирт.
2-Phenylethanol.
$C_6H_5CH_2CH_2OH$=122.2
CAS — 60-12-8.
UNII — ML9LGA7468.

Pharmacopoeias. In *Pol.* and *US*.

USP 36: (Phenylethyl Alcohol). A colourless liquid with a rose-like odour. Soluble 1 in 60 of water, 1 in less than 1 of alcohol, of chloroform, of ether, of benzyl benzoate, and of diethyl phthalate, and 1 in 2 of alcohol 50%; very soluble in glycerol, in propylene glycol, and in fixed oils; slightly soluble in liquid paraffin. Store in airtight containers in a cool, dry place. Protect from light.

Incompatibility. Phenethyl alcohol is incompatible with oxidising agents and proteins. Activity may be reduced by nonionic surfactants or by adsorption onto low density polyethylene containers.

Profile

Phenethyl alcohol is more active against Gram-negative than Gram-positive bacteria. It is used as a preservative in ophthalmic, nasal, and otic solutions at a concentration of 0.25 to 0.5%, usually with another bactericide, and up to 1% on its own in topical preparations. It is also used as an antiseptic in topical products in concentrations of up to 7.5%. It is also used as a component of flavouring essences and perfumes.

Phenethyl alcohol may cause eye irritation.

Antimicrobial action. Antimicrobial activity may be enhanced by the addition of phenethyl alcohol to solutions preserved with benzalkonium chloride, chlorhexidine acetate, phenylmercuric nitrate, chlorocresol, or chlorobutanol.[1]
1. Richards RME, McBride RJ. The preservation of ophthalmic solutions with antibacterial combinations. *J Pharm Pharmacol* 1972; **24**: 145–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Sebirinse; *Canad.*: Sclerodex; *Ger.*: Imazol; *India*: Borozin; *NZ*: Sebirinse; *UK*: Ceanel.

Phenol

Ácido carbólico; Ácido fénico; Carbolic Acid; Fenol; Fenoli; Fenolis; Hidroxibenceno; Phenic Acid; Phénol; Phenolum; Phenyl Hydrate; Phenylic Acid; Оксибензол; Фенол.
Hydroxybenzene.
C_6H_5OH=94.11
CAS — 108-95-2.
ATC — C05BB05; D08AE03; N01BX03; R02AA19.
ATC Vet — QC05BB05; QD08AE03; QN01BX03; QR02AA19.
UNII — 339NCG44TV.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Br., *Swiss*, and *US* also include a monograph for Liquefied Phenol.

Ph. Eur. 8: (Phenol). Colourless or faintly pink or faintly yellow deliquescent crystals or crystalline masses. F.p. not less than 39.5 degrees. Soluble in water; very soluble in alcohol, in dichloromethane, and in glycerol. Store in airtight containers. Protect from light.

BP 2014: (Liquefied Phenol). An aqueous mixture containing phenol 77.0 to 81.5% w/w in purified water. A colourless to faintly coloured, caustic liquid with a characteristic and not tarry odour. Soluble in water; miscible with alcohol, with ether, and with glycerol. Protect from light. It may congeal or deposit crystals if stored at a temperature below 4 degrees. It should be completely melted before use.

When phenol is to be mixed with collodion, fixed oils, or paraffins, melted phenol should be used, and not Liquefied Phenol.

USP 36: (Phenol). Colourless to light pink, interlaced or separate, needle-shaped crystals, or a white to light pink crystalline mass, with a characteristic odour. It gradually darkens on exposure to light and air. Soluble 1 in 15 of water; very soluble in alcohol, in chloroform, in ether, in glycerol, and in fixed and volatile oils; soluble 1 in 70 of liquid paraffin. A solution of 1 g in 15 mL water is clear and is neutral or acid to litmus. Store in airtight containers. Protect from light.

USP 36: (Liquefied Phenol). Phenol maintained in a liquid condition by the presence of about 10% of water; it contains not less than 89% by weight of phenol. It may contain a suitable stabiliser. A colourless to pink liquid which may develop a red tint upon exposure to air or light, and with a characteristic, somewhat aromatic odour. Miscible with alcohol, with ether, and with glycerol. Store in airtight glass containers. Protect from light.

When phenol is to be mixed with a fixed oil, liquid paraffin, or white soft paraffin, crystalline Phenol and not Liquefied Phenol should be used.

Incompatibility. Phenol is incompatible with alkaline salts and nonionic surfactants. The antimicrobial activity of phenol may be diminished through increasing pH or through combination with blood and other organic matter.

Use for preservation. NOTE. Phenol should not be used to preserve preparations that are to be freeze-dried.

Uses and Administration

Phenol is an antiseptic and disinfectant effective against vegetative Gram-positive and Gram-negative bacteria, mycobacteria, and some fungi, but only very slowly effective against spores. It is also active against certain viruses. Phenol is more active in acid solution.

Aqueous solutions up to 1% are bacteriostatic while stronger solutions are bactericidal.

Phenol is a commonly used antimicrobial preservative in parenteral preparations; concentrations of up to 0.5% are usually used.

A 0.5 to 1% solution has been used for its local anaesthetic effect to relieve itching.

A 1.4% solution is used for pain or irritation of the mouth and throat. Weak concentrations (up to 2%) have also been used topically for disinfection. A 5% solution has been used as a disinfectant for excreta.

Oily Phenol Injection (BP 2014), up to 10 mL, has been injected into the tissues around internal haemorrhoids as an analgesic sclerosing agent, but alternative procedures may be preferred. Aqueous phenol has also been used as a sclerosant in the treatment of hydroceles.

Solutions of phenol in glycerol have been given intrathecally for the alleviation of spasticity (p. 2014.2) or

injected intrathecally or into soft-tissue structures for the treatment of chronic low back pain. Other types of severe intractable pain may be relieved by injecting aqueous phenol close to motor nerves. Aqueous phenol has been used for chemical sympathectomy in peripheral vascular disorders and for the treatment of urinary incontinence.

Liquefied phenol has been used in the treatment of ingrowing toenails.

Dystonias. Phenol appears to produce a decrease in muscle tone without profound weakness and is considered to be an effective agent in treating focal dystonias.[1] Intramuscular phenol was reported[2] to have produced improvement in 2 adult patients with moderately severe spasmodic torticollis (p. 2019.2) who had not responded adequately to intramuscular injections of botulinum A toxin. Response was maintained by re-injection every 6 months. Following this case report, an open study[3] was conducted on 3 patients with spasmodic torticollis who had not responded to botulinum toxin A and other drug treatments. After 10 intramuscular injections of phenol, given weekly and then monthly, 2 of the patients showed improvement: one reached partial remission while the other had improvement that lasted for 3 months. The third patient did not respond to treatment with phenol. A study[4] to determine the efficacy and adverse effects of a 2% phenol block in patients with spasmodic torticollis was conducted in 16 patients, all of whom were refractory to oral drug and rehabilitation therapies. Results showed significant improvement in neck movement and position. However, 4 patients developed reversible sensory disturbance of the transverse cutaneous nerve of the neck area. A patient who developed a focal dystonic contraction of the foot responded to single intramuscular injection of 5% aqueous phenol, after initial treatment with botulinum toxin A had shown no benefit.[5]

1. Zafonte RD, Munin MC. Phenol and alcohol blocks for the treatment of spasticity. *Phys Med Rehabil Clin N Am* 2001; 12: 817–32.
2. Massey JM. Treatment of spasmodic torticollis with intramuscular phenol injection. *J Neurol Neurosurg Psychiatry* 1995; 58: 258–9.
3. García Ruiz PJ, Sanchez Bernardos V. Intramuscular phenol injection for severe cervical dystonia. *J Neurol* 2000; 247: 146–7.
4. Takeuchi N, *et al.* Phenol block for cervical dystonia: effects and side effects. *Arch Phys Med Rehabil* 2004; 85: 1117–20.
5. Kim J-S, *et al.* Idiopathic foot dystonia treated with intramuscular phenol injection. *Parkinsonism Relat Disord* 2003; 9: 355–9.

Haemorrhoids. Sclerotherapy with oily phenol injection has been used[1] to treat haemorrhoids (p. 1808.1). The technique for preventing mucosal prolapse is to inject small volumes (about 2 or 3 mL) of a 5% solution of phenol in arachis oil into the submucous space above each of the 3 principal haemorrhoids. Rather than causing the haemorrhoidal veins to thrombose, the injection works by producing submucosal fibrosis, fixing the mucosa to the underlying muscle. However, other techniques for mucosal fixation such as rubber band ligation or perhaps infrared coagulation are more effective and associated with fewer complications.[2-5]

1. Alexander-Williams J. The management of piles. *BMJ* 1982; 285: 1137–9.
2. Gartell PC, *et al.* A randomised clinical trial to compare rubber band ligation with phenol injection in the treatment of haemorrhoids. *Gut* 1984; 25: A563.
3. Ambrose NS, *et al.* Prospective randomised trial of injection therapy against photocoagulation therapy in first and second degree haemorrhoids. *Gut* 1984; 25: A563–4.
4. Johanson JF, Rimm A. Optimal nonsurgical treatment of hemorrhoids: a comparative analysis of infrared coagulation, rubber band ligation, and injection sclerotherapy. *Am J Gastroenterol* 1992; 87: 1601–6.
5. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities: a meta-analysis. *Dis Colon Rectum* 1995; 38: 687–94.

Ingrowing toenails. Liquefied phenol (88%) ablation has been performed as an alternative to surgical avulsion in the treatment of ingrowing toenails.[1,2] A systematic review[3] concluded that simple nail avulsion combined with treating the nail-bed with phenol was more effective at preventing symptomatic recurrence of ingrowing toenails than cutting out the nail-bed. However, there was a significant increase in postoperative infections when phenol was used.

1. Bostanci S, *et al.* Chemical matricectomy with phenol for the treatment of ingrowing toenail: a review of the literature and follow-up of 172 treated patients. *Acta Derm Venereol* 2001; 81: 181–3.
2. Andreassi A, *et al.* Segmental phenolization for the treatment of ingrowing toenails: a review of 6 years experience. *J Dermatol Treat* 2004; 15: 179–81.
3. Rounding C, Bloomfield S. Surgical treatments for ingrowing toenails. Available in The Cochrane Database of Systematic Reviews: Issue 1. Chichester: John Wiley; 2003 (accessed 15/03/06).

Pain. The neurolytic use of phenol to produce destructive nerve block (see under Pain, p. 1977.1) has produced variable results, and some consider the risk of complications outweighs the benefits. However, it may have the advantage over alcohol that it is painless on injection, and smaller volumes can be used, potentially allowing greater precision (see p. 1733.2).

Urinary incontinence. Although injection of phenol into the pelvic plexus to produce partial denervation has been used in the management of severe intractable urge incontinence, its use has been largely abandoned. Some patients, especially those with detrusor hyperreflexia, have derived benefit[1,2] but overall efficacy can be poor and benefits short-lived.[3]

1. Ewing R, *et al.* Suburigonal phenol injection therapy for incontinence in female patients with multiple sclerosis. *Lancet* 1983; i: 1304–5.
2. Blackford HN, *et al.* Results of transvesical infiltration of the pelvic plexuses with phenol in 116 patients. *Br J Urol* 1984; 56: 647–9.
3. Rosenbaum TP, *et al.* Trans-trigonal phenol failed the test of time. *Br J Urol* 1990; 66: 164–9.

Adverse Effects

When ingested, phenol causes extensive local corrosion, with pain, nausea, vomiting, sweating, and diarrhoea. Excitation may occur initially but it is quickly followed by unconsciousness. There is depression of the CNS, with cardiac arrhythmias, and circulatory and respiratory failure, which may lead to death. Acidosis may develop and occasionally there is haemolysis and methaemoglobinaemia with cyanosis. The urine may become dark brown or green. Pulmonary oedema and myocardial damage may develop, and damage to the liver and kidneys may lead to organ failure.

Severe or fatal poisoning may occur from the absorption of phenol from unbroken skin or wounds and suitable precautions should be taken to prevent absorption. Applied to skin, phenol causes blanching and corrosion, sometimes with little pain. Aqueous solutions as dilute as 10% may be corrosive.

Toxic symptoms may also arise through absorption of phenol vapour by the skin or lungs. Phenol throat spray may cause local oedema.

Cresols and other phenolic substances have similar effects.

Effects on the heart. A 10-year-old boy developed life-threatening premature ventricular complexes during the application of a solution of phenol 40% and croton oil 0.8% in hexachlorophene soap and water for chemical peeling of a giant hairy naevus.[1] Cardiac arrhythmias have been reported after the use of phenol for chemical face peeling.[2] They were also seen in 3 of 16 children who received phenol 5% as a neurolytic.[3]

1. Warner MA, Harper JV. Cardiac dysrhythmias associated with chemical peeling with phenol. *Anesthesiology* 1985; 62: 366–7.
2. Botta SA, *et al.* Cardiac arrhythmias in phenol face peeling: a suggested protocol for prevention. *Aesthetic Plast Surg* 1988; 12: 115–17.
3. Morrison JE, *et al.* Phenol motor point blocks in children: plasma concentrations and cardiac dysrhythmias. *Anesthesiology* 1991; 75: 359–62.

Effects on the kidneys. A 41-year-old man developed acute renal failure due to cutaneous absorption of phenol after falling into a shallow vat of industrial solvent containing 40% phenol in dichloromethane. No ingestion occurred. Other symptoms included 50% body-surface burns, cold extremities, nausea, vomiting, and respiratory distress. The patient required haemodialysis for 3 weeks; some abnormalities of renal function remained one year later.[1]

1. Foxall PJD, *et al.* Acute renal failure following accidental cutaneous absorption of phenol: application of NMR urinalysis to monitor the disease process. *Hum Toxicol* 1989; 9: 491–6.

Effects on the liver. Phenol-induced hepatotoxicity has been reported[1] in a 43-year-old man after injection sclerotherapy for haemorrhoids with 5% phenol in arachis oil. During treatment the patient had pain radiating to the penis, then later developed backache and haematuria, and 6 days later was admitted to hospital with jaundice. He recovered well and his liver enzymes returned to normal levels after 6 months.

1. Suppiah A, Perry EP. Jaundice as a presentation of phenol induced hepatotoxocity [sic] following injection sclerotherapy for haemorrhoids. *Surgeon* 2005; 3: 43–4.

Effects on sexual function. Three patients developed urinary symptoms and impotence which lasted up to one year after each receiving phenol 5% in arachis oil sclerotherapy for haemorrhoids.[1]

1. Bullock N. Impotence after sclerotherapy of haemorrhoids: case reports. *BMJ* 1997; 314: 419.

Effects on the throat. Acute life-threatening epiglottitis occurred in a 49-year-old woman after the use of a throat spray containing the equivalent of 1.4% phenol. The reaction may have been anaphylactic or due to a direct toxic effect of the spray.[1] The UK CSM[2] reported in 1990 that it had received 4 reports of oedema of the epiglottis and/or larynx leading to respiratory difficulties. While the condition was rare, the effects were severe; 1 patient died and 2 survived only after emergency hospital treatment.

1. Ho S-L, Hollinrake K. Acute epiglottitis and Chloraseptic. *BMJ* 1989; 298: 1584.
2. CSM. Chloraseptic throat spray and oedema of the epiglottis and larynx. *Current Problems 28* 1990. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024446&RevisionSelectionMethod=LatestReleased (accessed 17/06/10)

Treatment of Adverse Effects

If phenol has been swallowed, activated charcoal may be useful. Some sources suggest the cautious use of gastric lavage although this is generally inappropriate after ingestion of corrosive substances.

If phenol has been spilled on the skin removal of contaminated clothing and excess phenol should be followed by washing of the skin with glycerol or, alternatively, with copious amounts of water. Macrogol 300 and vegetable oils have also been used.

Contamination of the eyes should be treated by flooding with water or sodium chloride 0.9% only for at least 10 to 15 minutes.

The patient should be kept warm and given supportive treatment. Intravenous sodium bicarbonate should be given where there is metabolic acidosis.

Precautions

Solutions containing phenol should not be applied to large areas of skin or large wounds since sufficient phenol may be absorbed to give rise to toxic symptoms. Phenol should not be used as a throat spray in patients with epiglottitis, or in children aged under 6 years.

Pharmacokinetics

Phenol is absorbed from the gastrointestinal tract and through skin and mucous membranes. It is metabolised to phenylglucuronide and phenyl sulfate, and small amounts are oxidised to catechol and quinol which are mainly conjugated. The metabolites are excreted in the urine; on oxidation to quinones they may tint the urine dark brown or green.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Haemorol; *Canad.*: Antiseptic Salve†; P & S; *Chile*: Metapio; *NZ*: Haemorol; *S.Afr.*: Medi-Keel A; SB Aurico Ear Drops†; Septosol; *Thai.*: Pose-Cresol†; *UK*: Ultra Chloraseptic; *Ukr.*: Orasept (Opacetr); *USA*: Cheracol Sore Throat; Chloraseptic Kids Sore Throat Spray; Chloraseptic Sore Throat; Green Throat Spray; P & S; Phenaseptic; Red Throat Spray; Triaminic Sore Throat Spray; Ulcerease.

Multi-ingredient Preparations. *Arg.*: Aceite Esmeralda Moone; Callicida; Manzan; Piracalamina; Prurisedan Rosa; Prurisedan; *Austral.*: Ayrton's Chilblain†; EgoPsoryl TA; Nyal Toothache Drops; Sarna†; *Austria*: Herposicc; *Belg.*: Eucalyptine Pholcodine; Sedemol; Sulfa-Sedemol; *Braz.*: Cloraseptic; Dentisan†; Otoloide; *Canad.*: Ak Lip Balm†; Blistex DCT Lip Balm†; Blistex Lip Medex†; Blistex Medicated Lip Ointment†; Carmex Lip Balm; Carmex Lip Ointment; Lip Conditioner Lip Balm; Lip Medex†; Medicated Blistex DCT Lip Balm; Ozonol; *Chile*: Blistex; Chapstick Medicated; *China*: Posterisan (玻特利); *Fr.*: Aldyzine; Brulex; Otylol; Pulperyl; Rockles; Sedapulpe†; Solute Physiologique Phenole Lavoisier; Yranol Eugenole; *Hong Kong*: Cepastat; Egopsoryl TA; *Hung.*: Reparon; *Irl.*: Blistex Relief; Germolene First Aid; Germolene; TCP; TCP; *Ital.*: Creosoto Composto; Fucsina Fenica; Lavanda Sofar; Pinselina Knapp; *Malaysia*: Egopsoryl TA; Sarna; *Mex.*: Forcremol; *Neth.*: Agrc-Gola†; *NZ*: Egopsoryl TA; *Philipp.*: Calmoseptine; Sarna; *Rus.*: Fucaseptol (Фукасептол); *S.Afr.*: Adco-Biohist; Alpha Toothache Essence†; Blistex; Calasthetic; Germolene†; Prep†; SB Universal Ointment†; TCP†; *Singapore*: Calamine and Menthol; Castellani's Paint; Cepastat; Egopsoryl TA; Sarna; *Spain*: Dermomycose Liquido; Otocerum; Otogen Calmante; *Thai.*: Con Con; Lanol; Sarna; Zema; *Turk.*: Disinol; *UK*: Blistex Relief; Chymol; Colsor; Dermacreme; Germolene; Germolene; Germolene; Lacto Calamine; TCP; TCP; TCP; *USA*: Anbesol; Anbesol; Blistex Lip Balm; Blistex; Boil Base; Campho-Phenique; Castaderm; Cepastat Cherry; Cepastat; Chapstick Medicated Lip Balm; Columbia Antiseptic Powder; Debacterol; Heal Aid Plus; Lip Medex; Lipmagik; Massengill; Mycinette; Nasal Jelly; Orabase Lip; Orasol; Phylorinol; Phylorinol; Skeeter Stik; Sting-Eze; Unguentine Plus; Unguentine.

Homoeopathic Preparations. *Canad.*: Hylands Vaginitis†.

Pharmacopoeial Preparations

BP 2014: Aqueous Phenol Injection; Liquefied Phenol; Oily Phenol Injection; Phenol and Glycerol Injection;
BPC 1973: Magenta Paint;
USP 36: Camphorated Phenol Topical Gel; Carbol-Fuchsin Topical Solution; Liquefied Phenol; Phenolated Calamine Topical Suspension.

Phenoxyethanol

Ethylene Glycol 2-Monophenyl Ether; Ethyleneglycol Monophenylether; Fenoksietanoli; Fenoksietanolis; Fenoksyetanol; Fenoxietanol; Fenoxyethanol; Phenoxyaethanol;

Phénoxyéthanol; Phenoxyethanolum; 2-Phenoxyethyl Alcohol; β-Phenoxyethyl Alcohol; Феноксиэтанол. 2-Phenoxyethanol.

$C_8H_{10}O_2$=138.2

CAS — 122-99-6.

UNII — HIE492ZZ3T.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Phenoxyethanol). A colourless slightly viscous liquid. Slightly soluble in water, in arachis oil and in olive oil; miscible with alcohol, with acetone, and with glycerol.

USNF 31: (Phenoxyethanol). A colourless, slightly viscous liquid. Specific gravity 1.105 to 1.110 at 20 degrees. Slightly soluble in water; miscible with alcohol, with acetone, and with glycerol; slightly soluble in arachis oil and in olive oil. Store in a dry place, in airtight containers at a temperature of 8 degrees to 15 degrees. Protect from light.

Incompatibility. The activity of phenoxyethanol may be reduced by interaction with nonionic surfactants and possibly by adsorption onto PVC.

Profile

Phenoxyethanol is effective against strains of *Pseudomonas aeruginosa* but less so against other Gram-negative and Gram-positive bacteria. It has been used as a preservative in cosmetics and topical pharmaceuticals at a concentration of 0.5 to 1%. It is often used with other preservatives, commonly hydroxybenzoates, to obtain a wider spectrum of antimicrobial activity.

Phenoxyethanol is used in concentrations of about 2% as an antiseptic for minor infections of skin, wounds, and mucous membranes. Aqueous solutions may be prepared by shaking the phenoxyethanol with hot water until dissolved, then adjusting to final volume when cool. Preparation of the solution can be aided by propylene glycol.

Phenoxypropanol and chlorophenoxyethanol are related compounds used in topical preparations.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK:* Blactol Liquid.

Multi-ingredient Preparations. *Arg.:* Cicatul; Polviderm NF; *Austral.:* QV Flare Up; *Austria:* Octenisept; *Canad.:* Marcorodex; *Chile:* Eucerin Piel Grasa†; *Cz.:* Octenisept; *Fr.:* Alco-Aloe†; *Ger.:* Linola Wundgel; Octenisept; *Gr.:* Octenisept; *India:* Exomega; *Irl.:* Aidex†; *Ital.:* Decon Ovuli; Fitostimoline; *Mex.:* Fitoestimulina; Italdermol; *NZ:* Acnederm; *Pol.:* Octenisept; *Port.:* Fitocreme; *Rus.:* Octenisept (Октенисепт); *Singapore:* Esemdent; Octenisept; *Switz.:* Octenisept; *Ukr.:* Denebol Gel (Денебол Гель); Octenisept (Октенисепт); Oktenisept (Октенисепт); *USA:* Bodi Kleen; *Venez.:* Glizigen; Photoderm AKN.

Phenoxyisopropanol

Fenoxilsopropanol; Phenoxyisopropyl Alcohol. 1-phenoxypropan-2-ol.

$C_9H_{12}O_2$=152.2

CAS — 770-35-4.

UNII — 87CZY0NYTA.

Profile

Phenoxyisopropanol is used as a preservative and as an antiseptic in preparations for the treatment of acne, insect bites, and minor abrasions to the skin.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.:* Clearasil Daily Face Wash†.

Multi-ingredient Preparations. *Canad.:* Antiseptic Lotion†.

Phenylmercuric Salts

Fenilmercurio, sales.

Phenylmercuric Acetate

Fenilgyvsidabrio acetatas; Fenil-higany-acetat; Fenilmercurid acetato de; Fenylhydrargyriumacetat; Fenylkvicksilveracetat; Fenylorteciowy octan; Fenyylimerkuriasetaatti; Phenylhydrargyni acetas; Phenylhydrargyri Acetas; Phénylmercure, acétate de; Phenylqueckailber(II)-acetat; PMA; Фенилмеркурацетат; Фенилртутьацетат. (Acetato)phenylmercury.

$C_8H_8HgO_2$=336.7

CAS — 62-38-4.

UNII — OSX88361UX.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Phenylmercuric Acetate). A white or yellowish crystalline powder or small, colourless crystals. Slightly soluble in water; soluble in alcohol and in acetone. Protect from light.

USNF 31: (Phenylmercuric Acetate). A white to creamy-white, odourless, crystalline powder or small white prisms or leaflets. Soluble 1 in 180 of water, 1 in 225 of alcohol, 1 in 6.8 of chloroform, and 1 in 200 of ether; soluble in acetone. Store in airtight containers. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Borate *(rINN)*

Borato de fenilmercurio; Fenilgyvsidabrio boratas; Fenil-higany-borát; Fenilmercurio, borato de; Fenylhydrargyrium-borát; Fenylkvicksilverborat; Fenylorteciowy boran; Fenyylimerkuriboraatti; Hydrargyrum Phenyloboricum; Phenomerborum; Phenylhydrargyri Boras; Phénylmercure, Borate de; Phenylmercuriborat; Фенилмеркуборат.

$C_6H_5HgOH.C_6H_5HgOB(OH)_2$=633.2 or C_6H_5HgOH, $C_6H_5HgBO_2$=615.2

CAS — 8017-88-7 ($C_{12}H_{13}BHg_2O_4$); 6273-99-0 ($C_{12}H_{11}BHg_2O_3$); 102-98-7 ($C_6H_7BHgO_3$).

ATC — D08AK02.

ATC Vet — QD08AK02.

UNII — ZT1TTY3NGJ.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Phenylmercuric Borate). A compound consisting of equimolecular proportions of phenylmercuric orthoborate and phenylmercuric hydroxide ($C_{12}H_{13}BHg_2O_4$) or of the dehydrated form (metaborate, $C_{12}H_{11}BHg_2O_3$) or a mixture of the two compounds. Colourless shiny crystals or a white or slightly yellowish crystalline powder. Slightly soluble in water and in alcohol. Protect from light.

Incompatibility. The incompatibilities of phenylmercuric salts are described under Phenylmercuric Nitrate, below.

Phenylmercuric Nitrate

Basic Phenylmercury Nitrate; Fenilgyvsidabrio nitratas; Fenil-higany-nitrát; Fenilmercurio, nitrato de; Fenylhydrargyrium-nitrát; Fenylkvicksilvernitrat; Fenylorteci(II) azotan; Fenyylimerkurinitraatti; Phenylhydrargyri nitras; Phénylmercure, nitrate de; Phenylmercurinitrat; PMN; Фенилмеркурнитрат. Nitratophenylmercury.

$C_6H_5HgOH.C_6H_5HgNO_3$=634.4

CAS — 8003-05-2 ($C_6H_5HgOH.C_6H_5HgNO_3$); 55-68-5 ($C_6H_5HgNO_3$).

ATC — D09AA04.

ATC Vet — QD09AA04.

UNII — CG8692ZN74.

Pharmacopoeias. In *Eur.* (see p. vii) and *Int.* Also in *USNF.*

Ph. Eur. 8: (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white or pale yellow powder. Very slightly soluble in water and in alcohol; slightly soluble in hot water; dissolves in glycerol and in fatty oils. Protect from light.

USNF 31: (Phenylmercuric Nitrate). A mixture of phenylmercuric nitrate and phenylmercuric hydroxide. A white crystalline powder. Soluble 1 in 600 of water; slightly soluble in alcohol and in glycerol; more soluble in the presence of nitric acid or alkali hydroxides. A saturated solution in water is acid to litmus. Store in airtight containers. Protect from light.

Incompatibility. The activity of phenylmercuric salts may be reduced by interaction with compounds such as kaolin, magnesium trisilicate, starch, and talc.[1,2] Disodium edetate and sodium thiosulfate can also produce inactivation.[3] Sodium metabisulfite can lead to precipitation,[3] or chemical destruction,[4] but it can also produce increased activity.[3] Other incompatibilities include bromides, iodides (chlorides to a lesser extent), metals, and ammonia and its salts.[5] There can be adsorption onto rubber and some plastics[5,6] although sorption by low density polyethylene can be inhibited by phosphate ions.[7] Some filters, though not membrane filters, used for sterilisation removed considerable amounts of phenylmercuric nitrate from solution.[8] The pH may also affect activity.[9]

1. Yousef RT, *et al.* Effect of some pharmaceutical materials on the bactericidal activities of preservatives. *Can J Pharm Sci* 1973; 8: 54–6.
2. Horn NR, *et al.* Interactions between powder suspensions and selected quaternary ammonium and organomercurial preservatives. *Cosmet Toilet* 1980; 95: 69–73.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; 24 (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; 37 (suppl): 123P.
5. Matthews BR. Phenylmercuric nitrate. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association, 2009: 496–9.
6. Aspinall JA, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations. *J Clin Hosp Pharm* 1980; 5: 21–9.
7. Aspinall JE, *et al.* The effect of low density polyethylene containers on some hospital-manufactured eyedrop formulations II. Inhibition of the sorption of phenylmercuric acetate. *J Clin Hosp Pharm* 1983; 8: 233–40.
8. Naido NT, *et al.* Preservative loss from ophthalmic solutions during filtration sterilisation. *Aust J Pharm Sci* 1972; NS1: 16–18.
9. Wessels JMC, Adema DMM. Some data on the relationship between fungicidal protection and pH. In: Walters AH, Elphick JJ, eds. *Biodeterioration of materials.* Amsterdam: Elsevier, 1968: 517–23.

Uses

Phenylmercuric salts have antibacterial and antifungal properties. They are mainly bacteriostatic compounds although they also have a slow bactericidal action. Their activity has been reported to be pH dependent.

Phenylmercuric compounds are used as preservatives in cosmetic, ophthalmic, or pharmaceutical preparations and as antiseptics. They have also been used as spermicides.

As a preservative in eye drops, a concentration of 0.002% is usually used; in injection solutions, the concentration is usually 0.001%.

Adverse Effects and Precautions

While the adverse effects of inorganic mercury (p. 2556.1) should be taken into account when considering the adverse effects of phenylmercuric compounds, there is little evidence of systemic toxicity arising from their use. They are irritant to the skin and may give rise to erythema and blistering. Hypersensitivity reactions have been reported. Topical application to eyes has been associated with mercurialentis and atypical band keratopathy; prolonged use of eye drops containing phenylmercuric preservatives is not recommended.

Effects on the eyes. References to primary atypical band keratopathy and pigmentation of the anterior capsule of the lens (mercurialentis) associated with the prolonged use of eye drops containing phenylmercuric preservative.

1. Kennedy RE, *et al.* Further observations on atypical band keratopathy in glaucoma patients. *Trans Am Ophthalmol Soc* 1974; 72: 107–22.
2. Garron LK, *et al.* A clinical pathologic study of mercurialentis medicamentosus. *Trans Am Ophthalmol Soc* 1976; 74: 295–320.
3. Brazier DJ, Hitchings RA. Atypical band keratopathy following long-term pilocarpine treatment. *Br J Ophthalmol* 1989; 73: 294–6.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *India:* Kored; *USA:* Hem-Prep.

o-Phthaldialdehyde

o-Ftaldialdehído; o-Phthalaldehyde; Phtharal; o-Фталевый Альдегид. 1,2-Benzenedicarboxaldehyde.

$C_8H_6O_2$=134.1

CAS — 643-79-8.

UNII — 4P8QP9768A.

Uses and Administration

o-Phthaldialdehyde is a bactericidal disinfectant with similar actions to those of glutaral (p. 1753.2) but it is reported to be more active against mycobacteria and to be stable at a wider pH range of 3 to 9. Unlike glutaral it requires no activation before use.

A 0.55% aqueous solution of *o*-phthaldialdehyde is used for high-level disinfection of medical equipment that cannot be sterilised by heat. It is non-corrosive towards most materials. Complete immersion in the solution for a minimum of 12 minutes at 20 degrees or 5 minutes at 25 degrees or higher is recommended. For further details, see Disinfection of Endoscopes, p. 1731.2.

References.

1. Cooke RPD, *et al.* An evaluation of Cidex OPA (0.55% orthophthalaldehyde) as an alternative to 2% glutaraldehyde for high-level disinfection of endoscopes. *J Hosp Infect* 2003; 54: 226–31.

Adverse Effects and Precautions

As for Formaldehyde Solution, p. 1752.3.

Licensed product information states that *o*-phthaldialdehyde should not be used to process equipment used to treat patients with a history of bladder cancer as there have been associated rare reports of anaphylactoid reactions in such patients.

The symbol † denotes a preparation no longer actively marketed

Occupational exposure. For mention of the potential of *o*-phthaldialdehyde to cause sensitisation in those occupationally exposed, see under Peracetic Acid, p. 1763.2.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Cidex OPA; *USA*: Cidex OPA.

Picloxydine Dihydrochloride *(BANM, rINNM)*

Dihidrocloruro de picloxidina; Picloxydine, Dichlorhydrate de; Picloxydini Dihydrochloridum; Пиклоксидина Дигидрохлорид.

1,1′-[Piperazine-1,4-diylbis(formimidoyl)]bis[3-(4-chlorophenyl)guanidine] dihydrochloride.

$C_{20}H_{24}Cl_2N_{10}.2HCl$=548.3

CAS — 5636-92-0 (picloxydine); 19803-62-4 (picloxydine dihydrochloride).

ATC — S01AX16.

ATC Vet — QS01AX16.

Profile

Picloxydine is a biguanide disinfectant with properties similar to those of chlorhexidine (p. 1743.2). It is used in eye drops containing 0.05% of the dihydrochloride for the treatment of superficial infections of the eye. It has also been used as a surface disinfectant with quaternary ammonium compounds.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Vitabact; *Rus.*: Vitabact (Витабакт).

Polihexanide *(BAN, rINN)*

ICI-9073; Polihexanida; Polihexanidum; Polyaminopropyl Biguanide; Polyhexamethylene Biguanide Hydrochloride; Polyhexanide; Полигексанид.

Poly(1-hexamethylenebiguanide hydrochloride).

$(C_8H_{17}N_5.HCl)_n$

CAS — 32289-58-0.

ATC — D08AC05.

ATC Vet — QD08AC05.

UNII — 322U039GMF.

Profile

Polihexanide has antibacterial and antiamoebic activity. It is used as a surface disinfectant and for disinfecting soft contact lenses (p. 1730.2). It is also used in the treatment of *Acanthamoeba* keratitis (p. 919.3) and has also been tried as a mouthwash in dental care.

Bacterial vaginosis. A study[1] of the efficacy of a 2% polihexanide vaginal gel in the treatment of bacterial vaginosis found that a single application was comparable to that of a 2% clindamycin gel applied once daily for 7 consecutive days.

1. Gerli S, *et al.* A new approach for the treatment of bacterial vaginosis: use of polyhexamethylene biguanide: a prospective, randomized study. *Eur Rev Med Pharmacol Sci* 2003; **7**: 127–30.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Equate All-in-One; *Ger.*: Serasept; *Rus.*: Lavasept (Лавасепт); *Switz.*: Lavasept; *UK*: Prontosan.

Multi-ingredient Preparations. *Chile*: Biopiel; *Fr.*: Aniospray 29†; Hexanios G+R†; *Ger.*: Almyrol; Lavanid; Teta Extra†; Teta-S†; Urgosan.

Polynoxylin *(BAN, rINN)*

Polinoxilina; Polynoksylini; Polynoxyline; Polynoxylinum; Полиноксилин.

Poly[[bis(hydroxymethyl)ureylene]methylene].

$(C_4H_8N_2O_3)_n$

CAS — 9011-05-6.

ATC — A01AB05; D01AE05.

ATC Vet — QA01AB05; QD01AE05.

Profile

Polynoxylin is a condensation product of formaldehyde and urea. It is an antiseptic with antibacterial and antifungal actions and, like noxytiolin (p. 1762.1), may act by the release of formaldehyde. It is used topically for the local treatment of minor infections, usually at a concentration of 10%.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Gr.*: Anaflex; *Singapore*: Anaflex; *UK*: Anaflex.

Potassium Nitrate ⊗

Dusičnan draselný; E252; Kalii Nitras; Kalio nitratas; Kalium Nitricum; Kaliumnitraatti; Kaliumnitrat; Kálium-nitrát; Nitrato potásico; Nitre; Potassium, nitrate de; Potasu azotan; Saltpetre; Нитрат Калия.

KNO_3=101.1

CAS — 7757-79-1.

UNII — RU45X2JN0Z.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Potassium Nitrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.

USP 36: (Potassium Nitrate). Colourless crystals or a white crystalline powder. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol; soluble in glycerol. Store in airtight containers.

Nomenclature. The name saltpetre has been used as a generic term for a number of potassium- and sodium-based preservatives used in food manufacture. For a report of poisoning when a mixture of sodium nitrate and sodium nitrite was supplied for saltpetre, see p. 1769.3.

Uses and Administration

Potassium nitrate is used as a preservative in foods. It is also included in dentrifices to reduce the pain of hypersensitive teeth. When taken orally in dilute solution, it acts as a diuretic and was formerly used for this purpose.

Adverse Effects and Precautions

After ingestion potassium nitrate may be reduced to nitrite in the gastrointestinal tract by the action of bacteria and ingestion of large amounts can therefore cause methaemoglobinaemia. Gastrointestinal disturbances, vertigo, headache, flushing of the skin, hypotension, irregular pulse, cyanosis, convulsions, and collapse may occur. The toxic dose varies greatly; 15 g may prove fatal but much larger doses have been taken without serious effects. Poisoning has frequently been reported in infants given water from wells contaminated with nitrates.

Nitrites are precursors of nitrosamines, which are *animal* carcinogens, but a relationship with human cancer has not been established.

Concern has been expressed regarding the concentrations of nitrates and nitrites in the public drinking water supply. National limits are often set for permissible concentrations in drinking water.

Handling. Potassium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Sensodyne ProNamel; *Chile*: Crowne†; *India*: Accent; Aquadent-K; Arident; Dencare; Denex-P; Denex-PF; Denopot; Denoseal; Densafe; Dentra; Desflor; Emoform; K-Dent; Knit; Ledent; Magdent-K; Nitrodent-K; 02-Fresh; Orofact; *USA*: Denquel; Original Sensodyne.

Multi-ingredient Preparations. *Arg.*: Aquafresh Sensitive; Bucal Hyper Sensitive; Esmedent Dientes Sens Blanq + Ctrol Sarro; Esmedent Dientes Sensibles; Fluorogel 2001 para Dientes Sensibles; Kdesin; Sebulex; Sensident; Sensigel; Sensodyne Antisarro; Sensodyne Bicarbonato de Sodio; Sensodyne Blanqueador; Sensodyne Cool; Sensodyne Proteccion Total; Sensodyne-P; Teys's; *Braz.*: Malvatricin Dentes Sensiveis†; Sensodyne Antitartaro; Sensodyne C/Bicarbonato de Sodio; Sensodyne Cool†; Sensodyne Fresh Mint; Sensodyne Protecao Total; Sensodyne-F†; *Canad.*: Sensodyne-F; Sensodyne; *Chile*: Caristop Sensitive; Sensaid; *Fr.*: Emoform Dents Sensibles; Emoform Gencives; Fluocaril dents sensibles†; Sensigel; *India*: Denoseal-F; Denpot-KF; Dordent-K; Eydent K; Icee Mth Wsh; K-Dent-F; Klinit; Listn; Magdent-KF; Nitra-OR; Nitra; Nitrodent-KF; *Indon.*: Sensodyne Cool Gel; *Ital.*: Actisens; Dentosan Sensibile; Emoform Actisens; Fluocaril; Oral-B Denti Sensibili; *Mex.*: Cholal Modificado; Dentsiblen†; *Rus.*: Sensigel (Сенсигель); *Singapore*: 2Sensitive; Sensigel; *Turk.*: Sensodyne Gel; Sensoral; *UK*: Avoca; *USA*: Fluoridex Daily Defense Sensitivity Relief; Grafco; Sensitivity Protection Crest; Sensodyne iso-active; Sensodyne-F; *Venez.*: Sensodyne.

Homoeopathic Preparations. *Fr.*: Abbe Chaupitre no 1†; Urtica Complexe No 82†; *Ger.*: Pflugerplex Lemna; Phonix Silybum spag; Phonix Urtica-Arsenicum spag.

Pharmacopoeial Preparations

USP 36: Potassium Nitrate Solution.

Potassium Permanganate

Kalii Permanganas; Kalio permanganatas; Kalium Hypermanganicum; Kalium Permanganicum; Kaliumpermanganaat; Kaliumpermanganat; Kálium-permanganát; Manganistan draselný; Permanganato potásico; Pot. Permang.; Potassium, permanganate de; Potasu nadmanganian; Potasyum Permanganat; Калия Перманганат.

$KMnO_4$=158.0

CAS — 7722-64-7.

ATC — D08AX06; V03AB18.

ATC Vet — QD08AX06; QV03AB18.

UNII — 00OT1QX5U4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Potassium Permanganate). Dark purple or almost black crystals or a dark purple or brownish-black granular powder, usually with a metallic lustre. It decomposes in contact with certain organic substances. Soluble in cold water and freely soluble in boiling water.

USP 36: (Potassium Permanganate). Dark purple crystals, almost opaque by transmitted light and with a blue metallic lustre by reflected light; its colour is sometimes modified by a dark bronze-like appearance. Soluble 1 in 15 of water and 1 in 3.5 of boiling water.

Incompatibility. Potassium permanganate is incompatible with iodides, reducing agents, and most organic substances.

Uses and Administration

Potassium permanganate possesses oxidising properties which in turn confer disinfectant and deodorising properties. It is also astringent. Though bactericidal *in vitro* its clinical value as a bactericide is minimised by its rapid reduction in the presence of body fluids.

Solutions are used as cleansing applications to wounds, ulcers, or abscesses and as wet dressings and in baths in eczematous conditions and acute dermatoses especially where there is secondary infection. It is often prepared as a concentrated 0.1% solution in water to be diluted 1 in 10 before use to provide a 0.01% (1 in 10 000) solution. Solutions have also been used in bromhidrosis, in mycotic infections such as athlete's foot, and in poison ivy dermatitis.

Potassium permanganate is added to formaldehyde solution to produce formaldehyde vapour for the disinfection of rooms and cabinets (see p. 1752.2).

Adverse Effects, Treatment, and Precautions

The dry crystals or concentrated solutions of potassium permanganate are highly corrosive to tissue, while dilute solutions are mildly irritant. Contact with the skin causes irritation, redness, pain and burns, and even dilute solutions cause hardening of the outer layer of the skin and leave a brown stain on the skin. Exposure of the eye to dry crystals (including crystal dust) or concentrated solutions causes irritation, blurred vision, redness, brown staining of the conjunctiva, swelling of the eyelids, and corneal and conjunctival burns. For the effects of ingestion, see below.

The insertion into the vagina of potassium permanganate for its supposed abortifacient action causes corrosive burns, severe vaginal haemorrhage, and perforation of the vaginal wall, leading to peritonitis. Vascular collapse may occur.

Handling and storage. Potassium permanganate may be explosive if it is brought into contact with organic or other readily oxidisable substances. It has been used for the illicit preparation of fireworks; care is required with its supply.

Poisoning. Ingestion of dilute solutions of potassium permanganate may result in the mouth and throat being stained brown, sore throat, dysphagia, abdominal pain, diarrhoea, and vomiting. Ingestion of dry crystals and concentrated solutions causes oedema and necrosis of the mouth, larynx, gastrointestinal tract, and upper respiratory tract. In severe cases, acute respiratory distress syndrome, coagulopathy, hypotension, methaemoglobinaemia, hepatic necrosis, pancreatitis, and acute renal failure may develop. Oesophageal strictures and pyloric stenosis are possible long-term consequences. The fatal dose is probably about 10 g and death is usually as a result of pharyngeal oedema and cardiovascular collapse, although multiple organ failure may occur. Inhalation of potassium permanganate causes sore throat, coughing, and shortness

of breath. Chronic ingestion or inhalation of potassium permanganate has resulted in CNS symptoms such as sluggishness, sleepiness, weakness of the legs, tremor, spastic gait, and falling.

Symptoms of poisoning after ingestion of potassium permanganate should be treated symptomatically. Gut neutralisation and emesis are contra-indicated. Dilution with large quantities of water or milk is cautiously recommended, while the role of activated charcoal is unclear as it is unknown whether it binds potassium permanganate. Similarly, the role of corticosteroids is controversial and the efficacy of *N*-acetylcysteine for potassium permanganate hepatotoxicity is unproven. Eyes and skin contaminated with potassium permanganate should be thoroughly washed.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Turk.*: Permasol; *UK*: Permitabs.

Povidone-Iodine *(BAN)*

Iodinated Povidone; Jodowany powidon; Polivinilpirrolidona yodada; Polivodona yodada; Polyvidone-Iodine; Polyvinylpyrrolidone-Iodine Complex; Povidon-Iyot; Povidon, joderad; Povidon jodovaný; Povidona yodada; Povidonas, joduotas; Povidone iodée; Povidoni, jodattu; Povidon-jód; Povidonum iodinatum; Propyléneglycol, monostéarate de; PVP-Iodine; Повидон-йод.

CAS — 25655-41-8.

ATC — D08AG02; D09AA09; D11AC06; G01AX11; R02AA15; S01AX18.

ATC Vet — QD08AG02; QD09AA09; QD11AC06; QG01AX11; QG51AD01; QR02AA15; QS01AX18.

UNII — 85H0HZU99M.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Jpn*, and *US*.

Ph. Eur. 8: (Povidone, Iodinated). A complex of iodine with povidone containing 9 to 12% of available iodine calculated with reference to the dried substance. Yellowish-brown or reddish-brown amorphous powder. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone. A 10% solution in water has a pH of 1.5 to 5.0. Protect from light.

USP 36: (Povidone-Iodine). A complex of iodine with povidone containing 9 to 12% of available iodine calculated on the dried basis. A yellowish-brown to reddish-brown amorphous powder with a slight characteristic odour. It loses not more than 8% of its weight on drying. Soluble in water and in alcohol; practically insoluble in acetone, in carbon tetrachloride, in chloroform, in ether, and in petroleum spirit. Its solutions are acid to litmus. Store in airtight containers.

Incompatibility. Antimicrobial activity may be reduced at high pH.

Dermatological reactions, described as second- and third-degree burns, were seen in 4 patients in whom wounds were covered with a povidone-iodine soaked bandage secured to the skin by compound benzoin tincture. It was suggested that an interaction had occurred resulting in a more acidic pH.[1]

A mixture of povidone-iodine solution and hydrogen peroxide [brown bubbly] has caused explosions.[2]

1. Schillaci LJ, *et al.* Reduced pH associated with mixture of povidone-iodine and compound tincture of benzoin. *Am J Hosp Pharm* 1983; 40: 1694–5.
2. Dannenberg E, Peebles J. Betadine-hydrogen peroxide irrigation solution incompatibility. *Am J Hosp Pharm* 1978; 35: 525.

Uses and Administration

Povidone-iodine is an iodophore that is used as a disinfectant and antiseptic mainly for the treatment of contaminated wounds and pre-operative preparation of the skin and mucous membranes as well as for the disinfection of equipment.

Iodophores are loose complexes of iodine and carrier polymers. Solutions of povidone-iodine gradually release iodine to exert an effect against bacteria, fungi, viruses, protozoa, cysts, and spores; povidone-iodine is thus less potent than preparations containing free iodine but it is less toxic.

Many topical formulations are available, the majority containing about 4 to 10% of povidone-iodine; a 1% mouthwash has been used for oral infections including candidiasis and topical powders containing up to 2.5% povidone-iodine have been tried in the treatment and prevention of wound infection. For vaginal application povidone-iodine has also been used as pessaries containing 200 mg or as a 10% gel or solution.

Adverse Effects and Precautions

Povidone-iodine can cause hypersensitivity reactions and irritation of the skin and mucous membranes, although severe reactions are rare and povidone-iodine is considered to be less irritant than iodine.

The application of povidone-iodine to severe burns or to large areas otherwise denuded of skin may produce the systemic adverse effects associated with iodine (p. 2338.2) and metabolic acidosis, hypernatraemia, and renal impairment. Hyperthyroidism or hypothyroidism may occur after ingestion or absorption of large quantities. Hypothyroidism has occurred in neonates both as a result of absorption of iodine from povidone-iodine applied to the neonate and also to the mother during pregnancy or breast feeding. Povidone-iodine application is contra-indicated in premature neonates or those weighing less than 1.5 kg.

Regular or prolonged use should be avoided in patients with thyroid disorders or those receiving lithium therapy.

Acidosis. There have been reports of acidosis in patients whose burns were treated topically with povidone-iodine.[1,2] Fatal metabolic acidosis[3] and seizures[4] have been reported after mediastinal irrigation with povidone-iodine.

1. Pietsch J, Meakins JL. Complications of povidone-iodine absorption in topically treated burn patients. *Lancet* 1976; i: 280–2.
2. Scoggin C, *et al.* Hypernatraemia and acidosis in association with topical treatment of burns. *Lancet* 1977; i: 959.
3. Glick PL, *et al.* Iodine toxicity in a patient treated by continuous povidone-iodine mediastinal irrigation. *Ann Thorac Surg* 1985; 39: 478–80.
4. Zec N, *et al.* Seizures in a patient treated with continuous povidone-iodine mediastinal irrigation. *N Engl J Med* 1992; 326: 1784.

Breast feeding. Use of povidone-iodine in a vaginal gel by a breast-feeding woman resulted in elevated iodine concentrations in the breast milk and an odour of iodine on the infant's skin.[1] The American Academy of Pediatrics considers however that the use of povidone-iodine is usually compatible with breast feeding.[2]

For more on precautions in breast feeding when treated with iodine compounds see p. 2338.3.

1. Pastellon DC, Aranow R. Iodine in mother's milk. *JAMA* 1982; 247: 463.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 15/03/06)

Hypersensitivity. Immediate type I hypersensitivity reactions have been reported after topical disinfection with povidone-iodine; anaphylaxis has been reported after vaginal application[1,2] and after wound disinfection during surgery.[3] In some cases[2,3] skin tests showed that the reactions were caused by the povidone component.

Contact dermatitis has been reported[4] in a 36-year-old man who received a compress with 10% povidone-iodine aqueous solution under an occlusive bandage. The patient had mild itching, erythema, exudation, and a bullous reaction, limited to the area of the compress, 48 hours after application. He responded to topical corticosteroids within 5 to 6 days, but an area of sharply demarcated brown hyperpigmentation persisted for a month. While this was considered to be suggestive of an irritant effect, a positive patch test supported an allergic mechanism. A study to evaluate the incidence of contact dermatitis associated with povidone-iodine[5] found that 14 of 500 patients (2.8%) had a positive patch test with 10% povidone-iodine aqueous solution. On retesting with the same solution using a repeated open application test only 2 of the 14 (0.4%) were found to have true contact dermatitis to povidone-iodine.

1. Waran KD, Munsick RA. Anaphylaxis from povidone-iodine. *Lancet* 1995; 345: 1506.
2. Adachi A, *et al.* Anaphylaxis to polyvinylpyrrolidone after vaginal application of povidone-iodine. *Contact Dermatitis* 2003; 48: 133–6.
3. Le Pabic F, *et al.* First case of anaphylaxis to iodinated povidone. *Allergy* 2003; 58: 826–7.
4. Borja JM, *et al.* Contact dermatitis due to povidone-iodine: allergic or irritant? *J Investig Allergol Clin Immunol* 2003; 13: 131–2.
5. Lachapelle JM. Allergic contact dermatitis from povidone-iodine: a re-evaluation study. *Contact Dermatitis* 2005; 52: 9–10.

Neonates. Hypothyroidism has been reported in premature and very low birth-weight infants after the use of povidone-iodine for routine antisepsis,[1,2] and hyperthyroidism in a full-term infant following mediastinal lavage.[3]

Perinatal vaginal use of povidone-iodine may also cause neonatal thyroid dysfunction.[4]

1. Parravicini E, *et al.* Iodine, thyroid function, and very low birth weight infants. *Pediatrics* 1996; 98: 730–4.
2. Linder N, *et al.* Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *J Pediatr* 1997; 131: 434–9.
3. Bryant WP, Zimmerman D. Iodine-induced hyperthyroidism in a newborn. *Pediatrics* 1995; 95: 434–6. Correction. *ibid.*; 96: 779.
4. l'Allemand D, *et al.* Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine. *J Pediatr* 1983; 102: 935–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Antiseptico; Excelentia Solucion *Antiseptica; Extraleci; Iodep; Iodomax;* Iopox; Nu-Gel Hidrogel en Placa†; Pervinox D; Pervinox; Povi Complex; Povibac; Povicler; Povitiol; Tycoytycoy; ***Austral.***: Betadine; Microshield PVP-S†; Microshield PVP; Nyal Medithroat Gargle; Savlon Antiseptic†; ***Austria***: Betadona; Betaisodona; Betaseptic Braunol; Braunovidon; Wundesin; ***Belg.***: Braunodine†; Braunol; Iodex; Iso-Betadine; ***Braz.***: Curativ; Laboriodine†; Marcodine; ***Canad.***: Betadine; Proviodine; Solunet 1†; Soluprep Povidone Iodee†; Spray I Dene†; ***Chile***: Difexon; ***China***: Ai Di Er (艾迪尔); Ai Ni Ya (艾妮亚); AiLiKe (艾利克); Dai Wei (黛卫); Li Le (丽乐); Li Ze (丽泽); Ri Jie Ning (日洁宁); Yi Su Xin (怡速欣); Cz.: Betadine; Braunol; Braunovidon; Jodisol; ***Fin.***: Betadine; ***Fr.***: Betadine; Betaseptic†; Polliodine†; ***Ger.***: Betaisodona; Braunol; Braunovidon; Mercuchrom-Jod; Polydona; Polysept; PVP-Jod; Sepso J; Traumasept; ***Gr.***: Betadine; Betarem; Drapix; Eva Povi; Evinolut; Igiol; Iodovine; Jodocourir; Libidon; Lombocid; Oxisept; Poviodine; Tinsole; ***Hong Kong***: Betadine; Freka-cid†; Proviodine†; Videne; ***Hung.***: Betadine; Braunovidon; Colpo-Cleaner; ***India***: Aglodine; Alphadine; Balvidine; Bestodin; Betadine-AD; Betadine; Betakind; Betasym; Cadine; Cipladine; Curedine; Dovidone; Enodine-S; Byedin; Intadine; Intodine; Iocandin; Iodolan; Lakdine; Medidine; Metpo; Microdine; Microshield PVP-S; Microshield PVP; Ovidine; Povidine; Wokadine; ***Indon.***: Abodine†; Asepta†; Betadine; Corsasep; Duvodine†; Erphaseptan; Porinfec; Isodine; Molexdine; Mugisept; Neo Iodine; Orodin; Scansepta; Septadine; Vidisep; ***Irl.***: Betadine; Braunol†; Braunosan†; Braunovidon†; Inadine; Savlon Dry; Videne; ***Israel***: Idovit†; Iodicare; Iodiflor; Iodispray; Iodo-Vit; Polydine; Polysept; Polyskin; PovEyeOdine; ***Ital.***: Asepsan; Betadine; Betaseptic; Braunol; Citro Jod; Destrobac; Eso-Jod; Esoform Jod 75; Farmaiod; Gammadin†; Golasept; Inadine; Iodosteril†; Iodoten; Jodocur; Jodogard†; Oftasteril; Poviderm; ***Jpn***: Finish†; Isodine; ***Malaysia***: Betadine; Freka-cid†; Poviderm; Septi-Aid†; Summer's Eve Medicated; ***Mex.***: Isodine; Losine; Yodacua†; Yodine; ***Neth.***: Betadine; Braunol; ***NZ***: Betadine; Biodil†; Riodine; ***Philipp.***: Bacticide; Betadine; Doseptidone; Povidine; Zigmadone; ***Pol.***: Betadine; Braunovidon; Jodi; Polodina-R; Polseptol†; PV Jod; ***Port.***: Betadine; Braunol; Ectodine; Ginoseptil†; Iodolab; Isodine†; Septil; ***Rus.***: Aquazan (Аквазан); Betadine (Бетадин); Iodovidon (Йодовидон); Iodoxyd (Йодоксид); Jodosept (Йодосепт); Wokadine (Вокадин)†; ***S.Afr.***: Betadine; Dermadine; Drygel†; Podine; Septadine; Septisooth; Steridine; Zedchem PVP-I; ***Singapore***: Betadine; ***Spain***: Acydona; Betadine; Betatul; Curadona; Heridine†; Iodina; Normovidona; Orto Dermo P†; Sanoyodo; Topionic; ***Switz.***: Betadine; Braunol; Braunosan H Plus†; Braunosan†; Braunovidon; Destrobac; Jodoplex; ***Thai.***: Annadine†; Bactedene; Betadine; Betamed; Eprodine; Freka-cid†; Ipodine; Isodine; Movidone†; P-Vidine; Pactadine; Pharmadine; Povadine; Povi-odine; Povidine; Pyrad-Povidone; Sepfadine; Septidine; Septyl; Upodine; Videne; X-Tardine; ***Turk.***: Batiodin; Batticon; Betakon; Biokadin; Isosol; Polyod; Poviiodex; Poviod; Poviseptin; Soliyod; Summer's Eve Medicated; ***UK***: Betadine; Inadine; Savlon Dry; Videne; ***Ukr.***: Betadine (Бетадин); Iodoxide (Йодоксид); Povisep (Повисеп); Ranostop (Рановстоп); Wokadine (Вокадин); ***USA***: ACU-dyne; Betadine; Biodine; Efodine; GRX Dyne; Iodex; Massengill Medicated; Minidyne; Operand; Polydine; Summer's Eve Medicated; Yeast-Gard Medicated; ***Venez.***: Betadine; Intradine; Intradyn; Norlidine.

Multi-ingredient Preparations. *Arg.*: Merthiolate Iodopovidona; *Belg.*: Braunoderm; *Cz.*: Jox; *Ger.*: Betaseptic; Braunoderm; Repithel; *India*: Atodine-M; Balvidine-M; Bestodin-M; Cezel-PT; Dinemet-M; Drez; E-Dine-M; Ecoseptic; Eczo-Wokadine; Fastaid; Flotears; Healin; Iocandin Sol; Iocandin-M; Lacrisol; Metro Plus; Metro-P; Metrogyl-P; Metrokind-P; Mezodin; Misodine-M; Ovidine-M; ***Indon.***: Kalpanax; Kopamex†; ***Irl.***: Braunoderm†; ***Ital.***: Braunoderm; Jodieci; ***Jpn***: U-Pasta; ***Mex.***: Bano Coloide; Riban; ***Port.***: Braunoderm†; ***Rus.***: Jox (Йокс); ***Switz.***: Betaseptic; Braunoderm; Jodoplex Teinture†; ***Ukr.***: Jox (Йокс); *USA*: Anbesol; Orasol; ProTech.

Pharmacopoeial Preparations

BP 2014: Povidone-Iodine Eye Drops; Povidone-Iodine Mouthwash; Povidone-Iodine Solution;

USP 36: Povidone-Iodine Cleansing Solution; Povidone-Iodine Ointment; Povidone-Iodine Topical Aerosol; Povidone-Iodine Topical Solution.

Propamidine Isetionate *(BANM, rINNM)*

Isetionato de propamidina; M&B 782; Propamidina, isetionato de; Propamidine Isethionate; Propamidine, Isétionate de; Propamidini Isetionas; Пропамидина Изетионат.

4,4'-Trimethylenedioxydibenzamidine bis(2-hydroxyethanesulphonate).

$C_{19}H_{28}N_4O_{10}S_2$=564.6

CAS — 104-32-5 (propamidine); 140-63-6 (propamidine isetionate).

ATC — D08AC03; S01AX15.

ATC Vet — QD08AC03; QS01AX15.

UNII — 7T9U84C42.

Profile

Propamidine isetionate is an aromatic diamidine antiseptic that is active against Gram-positive bacteria, but less active against Gram-negative bacteria and spore-forming organisms. It also has antifungal properties and is active against *Acanthamoeba*. Ophthalmic solutions containing 0.1% of propamidine isetionate are used for the treatment of conjunctivitis and blepharitis.

Acanthamoeba keratitis. The optimal regimen for the treatment of *Acanthamoeba* keratitis (p. 919.3) has yet to be determined. Propamidine isetionate applied topically was the first drug used with some success.[1,2] It was used with an aminoglycoside such as neomycin or a neomycin-polymyxin-gramicidin preparation and a cure was achieved in about 50% of cases. However, most cysts are resistant to neomycin and due to surface toxicity and poor *in-vitro* sensitivity, neomycin is no longer recommended.[2] Propamidine was later used with chlorhexidine or polihexanide. However, poor cysticidal activity, chronic conjunctival infection, and resistance of some strains of *Acanthamoeba* to propamidine has prompted the suggestion that it should be replaced by another diamidine such as hexamidine.[3]

1. Murdoch D, *et al.* Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. *Aust N Z J Ophthalmol* 1998; 26: 231–6.
2. Seal DV. Acanthamoeba keratitis update—incidence, molecular epidemiology and new drugs for treatment. *Eye* 2003; 17: 893–905.
3. Perrine D, *et al.* Amoebicidal efficiencies of various diamidines against two strains of Acanthamoeba polyphaga. *Antimicrob Agents Chemother* 1995; 39: 339–42.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Brolene; *Gr.*: Brolene; *Irl.*: Brolene; Golden Eye; *NZ*: Brolene; *S.Afr.*: Brolene; *UK*: Brolene; Golden Eye Drops.

Propiolactone *(BAN, USAN, rINN)*

BPL; NSC-21626; 2-Oxetanone; Propanolide; Propiolactona; β-Propiolactone; Propiolactonum; Пропиолактон.
Propiono-3-lactone.
$C_3H_4O_2$=72.06
CAS — 57-57-8.
UNII — 6RC3ZT4HB0.

Profile

Propiolactone vapour is an irritant, mutagenic, possibly carcinogenic, disinfectant which is very active against most micro-organisms including viruses. It is rather less effective against bacterial spores.

Propiolactone vapour has been used for the gaseous sterilisation of pharmaceutical and surgical materials and for disinfecting large enclosed areas. It has low penetrating power. Propiolactone liquid has also been used.

Propyl Alcohol

Alcohol propílico; Normal Propyl Alcohol; Primary Propyl Alcohol; 1-Propanol; Propanol; Propanoli; Propanolis; Propanolum; Пропиловый Спирт.
Propan-1-ol.
$CH_3CH_2CH_2OH$=60.10
CAS — 71-23-8.
ATC — D08AX03.
ATC Vet — QD08AX03.
UNII — 96F264O9SV.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Propanol). A clear colourless liquid. Miscible with water and with dehydrated alcohol. Protect from light.

Uses and Administration

Propyl alcohol, an antiseptic with properties similar to those of alcohol (p. 1733.2), is used in preparations for disinfection of the hands, skin, surfaces, and instruments.

Isopropyl alcohol (p. 1758.3) is also used as an antiseptic.

Adverse Effects and Treatment

As for Alcohol, p. 1733.3; propyl alcohol is considered more toxic.

References.
1. WHO. 1-Propanol. *Environmental Health Criteria 102.* Geneva: WHO, 1990. Available at: http://www.inchem.org/documents/ehc/ehc/ehc102.htm (accessed 15/03/06)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Ger.*: Skinman Asept†; Skinman clear.

Multi-ingredient Preparations. *Austria*: Dodesept; Isozid-H; Kodan; Marcocid; Octeniderm; Sterillium; *Belg.*: Softa Man; *Canad.*: Manorapid Synergy; *Fin.*: Sterillium; *Fr.*: Anios DD†; Sterillium; *Ger.*: Aerodesin; Bacillol AF; Bacillol Foam; Bacillol plus; Bacillol Tissues; Bacillol Wipes; Bacillol†; Preka-Steril†; HD 410; Hospisept; Incidin; Incidin; Kodan Tinktur Forte; Manusept viruzid†; Meliseptol Rapid; Meliseptol; Softa Man; Sterillium; Virusept†; *Gr.*: Chiro Des; Octeniderm; Sterillium; *Irl.*: Sterillium; *Ital.*: Softa Man; *Neth.*: Softa-Man; Sterillium; *Port.*: Sterillium; *Singapore*: Listerine Bright & Clean; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Primasept Med; *Swed.*: Sterillium; *Switz.*: Kodan forte; Octeniderm; Softa-Man†; *Ukr.*: Softa-Man (Софта)†.

Ritiometan *(rINN)*

Ritiometán; Ritiométan; Ritiometanum; Ритиометан.
(Methylidynetrithio)triacetic acid.
$C_7H_{10}O_6S_3$=286.3
CAS — 34914-39-1.
ATC — R01AX05.
ATC Vet — QR01AX05.
UNII — J89LM8QVEE.

Profile

Ritiometan is used as the magnesium salt in an aerosol preparation for the treatment of infections of the nose and throat.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Fr.*: Necyrane.

Scarlet Red

Biebrich Scarlet R Medicinal; CI Solvent Red 24; Colour Index No. 26105; Fat Ponceau R; Rojo escarlata; Rojo Sudán IV; Rubrum Scarlatinum; Scharlachrot; Sudan IV; Судан IV.
1-[4-(o-Tolylazo)-o-tolylazo]naphth-2-ol.
$C_{24}H_{20}N_4O$=380.5
CAS — 85-83-6.

Profile

Scarlet red is an antiseptic dye that has been used topically. It can be irritant. Scarlet red is not permitted as a food colour in the EU, as it is thought to be a genotoxic carcinogen.

Sodium Azide

Azida sódica; Sodu azydek; Азид Натрия.
N_3Na=65.01
CAS — 26628-22-8.

Uses

Sodium azide has been used as an antimicrobial preservative in laboratory reagents, serum samples, and dialysis equipment. It is also used in car airbags; sudden impact triggers an electrical charge causing the sodium azide to explode and nitrogen gas is released.

Adverse Effects and Precautions

Sodium azide is a potent vasodilator and the most common adverse effect, regardless of the route of exposure, is hypotension. Hypotension developing more than an hour after exposure is associated with more severe toxicity and fatality. Other severe symptoms include seizure, coma, arrhythmia, tachypnoea, pulmonary oedema, metabolic acidosis, and cardiorespiratory arrest. Milder symptoms include nausea, vomiting, diarrhoea, headache, dizziness, temporary loss of vision, palpitations, dyspnoea, temporary loss of consciousness, or decreased mental status. There is no specific antidote for sodium azide intoxication.

Solutions containing sodium azide must not be disposed of into drain pipelines containing copper, lead, or brass since highly explosive heavy metal azides may be produced.

References to acute poisoning with sodium azide.

1. Edmonds OP, Bourne MS. Sodium azide poisoning in five laboratory technicians. *Br J Ind Med* 1982; 39: 308–9.
2. Klein-Schwartz W, *et al.* Three fatal sodium azide poisonings. *Med Toxicol Adverse Drug Exp* 1989; 4: 219–27.
3. Anonymous. Sodium azide contamination of hemodialysis water supplies. *JAMA* 1989; 261: 2603.
4. Chang S, Lamm SH. Human health effects of sodium azide exposure: a literature review and analysis. *Int J Toxicol* 2003; 22: 175–86.

Airbag deployment. Chemical and thermal burns have occurred after accidental perforation of airbags in motor vehicles and the release of sodium azide and other byproducts. Irritant contact dermatitis usually affecting the upper chest, arms, and face, and blunt trauma have also been reported.[1,2]

1. Corazza M, *et al.* Effects of airbag deployment: lesions, epidemiology, and management. *Am J Clin Dermatol* 2004; 5: 295–300.
2. Suhr M, Kreusch T. Burn injuries resulting from (accidental) airbag inflation. *J Craniomaxillofac Surg* 2004; 32: 35–7.

Effects on the nervous system. A study[1] to evaluate occupational neurotoxicity to sodium azide over a period of 5 years found that the only significant chronic symptom was trembling of the hands, occurring in 15 of 41 exposed workers compared with none of 42 controls. There was no difference between the 2 groups for other psychological or neuropsychological tests. Acute adverse effects most commonly reported by the exposed workers were heart palpitations, fatigue, nausea, vertigo, and irritated or red eyes.

1. Miljours S, Braun CMJ. A neuropsychotoxicological assessment of workers in a sodium azide production plant. *Int Arch Occup Environ Health* 2003; 76: 225–32.

Haemodialysis. Of 10 investigations by the CDC[1] into outbreaks of disease caused by chemicals in haemodialysis facilities between 1979 and 1999, one was due to sodium azide. Inadequate rinsing of water filters resulted in the exposure of 9 patients to sodium azide in a dialysis centre. Patients experienced sudden hypotension, blurred vision, headache, nausea, vomiting, syncope, and 1 patient had cramps.

1. Arduino MJ. CDC investigations of noninfectious outbreaks of adverse events in hemodialysis facilities, 1979-1999. *Semin Dial* 2000; 13: 86–91

Sodium Diacetate

Diacetato de sodio; E262; Диацетат Натрия.
Sodium hydrogen diacetate.
$CH_3COONa,CH_3COOH(+xH_2O)$
CAS — 126-96-5 (anhydrous sodium diacetate).
UNII — 26WJH3CS0B.

Profile

Sodium diacetate is used as a preservative in foods, particularly as an inhibitor of moulds and rope-forming micro-organisms in bread.

Sodium Formaldehyde Sulfoxylate

Formaldehído sulfoxilato sódico; Natrii Formaldehydosulfoxylas; Sodium Formaldehyde Sulphoxylate; Sodu formaldehydosulfoksylan; Натрия Формальдегидсульфоксилат.
Sodium hydroxymethanesulphinate dihydrate.
$CH_3NaO_3S,2H_2O$=154.1
CAS — 149-44-0 (anhydrous sodium formaldehyde sulfoxylate); 6035-47-8 (sodium formaldehyde sulfoxylate, dihydrate).
UNII — X4ZGP7K714.

Pharmacopoeias. In *Pol.* Also in *USNF.*

USNF 31: (Sodium Formaldehyde Sulfoxylate). White crystals or hard white masses with the characteristic odour of garlic. Soluble 1 in 3.4 of water, 1 in 510 of alcohol, 1 in 175 of chloroform, and 1 in 180 of ether; slightly soluble in benzene. A 2% solution in water has a pH of 9.5 to 10.5. Store at 15 degrees to 30 degrees. Protect from light.

Profile

Sodium formaldehyde sulfoxylate is an antoxidant used as a preservative in pharmaceuticals. It has been used in the treatment of acute mercury poisoning (p. 2556.3).

Sodium Hypochlorite

Hipoclorito sódico; Lejía; Гипохлорит Натрия.
$NaOCl,5H_2O$=164.5
CAS — 7681-52-9.
ATC — D08AX07.
ATC Vet — QD08AX07.
UNII — DY38VHM5OD.

NOTE. The term 'liquid chlorine' (Cloro líquido) has been used for solutions of sodium hypochlorite. These should not be confused with the pressurised form of chlorine gas (p. 1746.2) which is also liquid and has been referred to similarly.

Pharmacopoeias. *Br.*, *Fr.*, and *US* include sodium hypochlorite solutions.

BP 2014: (Dilute Sodium Hypochlorite Solution). It contains 1% of available chlorine. Store away from acids at a temperature not exceeding 20 degrees. Protect from light.

BP 2014: (Strong Sodium Hypochlorite Solution). It contains not less than 8% of available chlorine. It should be diluted before use. Store away from acids at a temperature not exceeding 20 degrees. Protect from light.

USP 36: (Sodium Hypochlorite Solution). It contains not less than 4% and not more than 6% w/w of anhydrous sodium hypochlorite. It is not suitable for application to wounds. Store in airtight containers. Protect from light.

USP 36: (Sodium Hypochlorite Topical Solution). It contains 0.025% sodium hypochlorite. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of hypochlorites is rapidly reduced in the presence of organic material; it is also pH dependent being greater in acid pH although hypochlorites are more stable at alkaline pH.

Sodium hypochlorite solutions should not be mixed with solutions of strong acids or ammonia; the subsequent reactions release chlorine gas and tosylchloramide sodium gas, respectively.

Stability. The stability of sodium hypochlorite solutions increases with pH, solutions of pH 10 or more being most stable.[1] Stability studies have shown that solutions providing 0.04 to 0.12% 'available chlorine' stored in amber glass bottles at room temperature could carry a 23-month expiry date.[2]

1. Bloomfield SF, Sizer TJ. Eusol BPC and other hypochlorite formulations used in hospitals. *Pharm J* 1985; 235: 153–5 and 157.
2. Fabián TM, Walker SE. Stability of sodium hypochlorite solutions. *Am J Hosp Pharm* 1982; 39: 1016–17.

Uses and Administration

Sodium hypochlorite is a disinfectant and antiseptic with the brief and rapid actions of chlorine (see p. 1746.3). Sodium hypochlorite pentahydrate contains about 43% of 'available chlorine' (see p. 1746.3); anhydrous sodium hypochlorite contains about 95%. Powders and solutions are commonly used for the rapid disinfection of hard surfaces (see Disinfection in Creutzfeldt-Jakob Disease, p. 1730.3 and in Hepatitis and HIV Infection, p. 1731.2), food and dairy equipment, babies' feeding bottles, excreta, and water (p. 1731.3). Solutions for use as domestic bleaches contain up to 5.25% of hypochlorite. Only diluted solutions containing up to 0.5% of 'available chlorine' are suitable for use on the skin and in wounds (but see Wound Disinfection, p. 1732.2). Sodium hypochlorite solutions ranging from 0.5 to 5.25% are used in dentistry for root canal irrigation.

Solutions of hypochlorites used as disinfectants have included Labarraque's Solution containing sodium hypochlorite with an alkali, and Eau de Javel, containing sodium or potassium hypochlorite.

Disinfection. *INSTRUMENTS.* Needles and syringes should not usually be sterilised chemically. However, cleaning of injection equipment with hypochlorite has been suggested as a last resort in the absence of sterile equipment, to reduce the risk of HIV transmission associated with the enforced re-use of injection equipment by injection drug users.[1] Use of full-strength domestic bleach (about 5% sodium hypochlorite, about 2% of 'available chlorine') was reported to be effective for the cleaning of intravenous drug users' equipment; a 30-second contact time was required.[1,2] A 1 in 10 dilution of bleach was not effective after exposure for 5 minutes.[2] Despite rinsing with water, a low residual concentration of hypochlorite and microaggregates of blood are likely to remain on the cleaned instruments. Free chlorine is a potent oxidant and low concentrations of oxidants have been shown to enhance tissue inflammation *in vivo* as well as HIV-1 replication *in vitro*. This has led some researchers to suggest that there may be an increased possibility of an injection drug user contracting HIV-1 through the sharing of a bleach-cleaned blood-contaminated syringe as a consequence of the concomitant transmission of residual bleach; however, there is no epidemiological evidence to confirm this.[3]

1. Donoghoe MC, Power R. Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; 341: 1658.
2. Watters JK, *et al.* Household bleach as disinfectant for use by injecting drug users. *Lancet* 1993; 342: 742–3.
3. Contoreggi C, *et al.* Effects of varying concentrations of bleach on in vitro HIV-1 replication and the relevance to injection drug use. *Intervirology* 2000; 43: 1–5.

WORMS. Sodium hypochlorite in aqueous solution at a concentration of 3.75% (or greater) is an effective ovicide for *Echinococcus* and may be used on hard surfaces, glassware, and sinks.[1]

1. Craig PS, Macpherson CNL. Sodium hypochlorite as an ovicide for Echinococcus. *Ann Trop Med Parasitol* 1988; 82: 211–13.

WOUNDS. Hypochlorite solutions are now generally considered to be too irritant for use in the management of wounds (p. 1690.1). Studies suggest that they may delay wound healing if repeatedly applied to open wounds.[1,2] It has been suggested that they may be of use in debriding burns (p. 1683.1) or necrotic chronic wounds,[3] but also that any benefit that might be seen from the desloughing of necrotic tissue might be produced by damage of the superficial cell layer leading to separation[4] or from tissue hydration produced by wet dressing packs.[5] However, some burns units have found that hypochlorite as Dakin's solution (see Chlorinated Lime, p. 1746.2) produces better healing than other antibacterials.[6]

See also p. 1732.2.

1. Thomas S, Hay NP. Wound healing. *Pharm J* 1985; 235: 206.
2. Lineweaver W, *et al.* Topical antimicrobial toxicity. *Arch Surg* 1985; 120: 267–70.
3. Leaper DJ, Eusol. *BMJ* 1992; 304: 930–1.
4. Anonymous. Local applications to wounds—I: cleansers, antibacterials, debriders. *Drug Ther Bull* 1991; 29: 93–5.
5. Thomas S. Milton and the treatment of burns. *Pharm J* 1986; 236: 128–9.
6. Murphy KD, *et al.* Current pharmacotherapy for the treatment of severe burns. *Expert Opin Pharmacother* 2003; 4: 369–84.

Adverse Effects

Hypochlorite solutions release hypochlorous acid upon contact with gastric juice and acids. Most patients ingesting hypochlorites will develop only mild gastrointestinal irritation. However, ingestion of small amounts of 3 to 5% hypochlorite solutions may result in irritation of the oropharynx, a burning sensation in the mouth and throat, and thirst. Nausea, vomiting, and haematemesis may occur. Ingestion of large amounts or more concentrated solutions causes irritation and corrosion of mucous membranes with chest and abdominal pain and tenderness, vomiting, haematemesis, watery diarrhoea and sometimes melaena. Ingestion of extremely large volumes may rarely cause hypernatraemia, hyperchloraemia, hypotension, and changes in mental status. In very severe cases ulceration or perforation of the oesophagus or stomach may occur leading to haemorrhage and shock.

Inhalation of the fumes is irritant to the eyes, nose, and respiratory tract. Sore throat, cough, bronchoconstriction, headache, ataxia, and confusion may develop. In severe cases dyspnoea and stridor due to laryngeal oedema may develop with breathlessness, wheeze, hypoxia, cyanosis, pneumonitis, and pulmonary oedema.

Hypochlorite solutions may be irritating to the skin and allergic contact dermatitis has been reported. Hypochlorite solutions may cause an alkali-type burn when splashed into the eye.

General references.

1. Racioppi F, *et al.* Household bleaches based on sodium hypochlorite: review of acute toxicology and Poison Control Center experience. *Food Chem Toxicol* 1994; 32: 845–61.

Effects on the blood. A child with G6PD deficiency had an acute haemolytic crisis after swimming for about 4 hours in an indoor pool containing very high concentrations of sodium hypochlorite.[1]

1. Ong SJ, Kearney B. Local swimming pool and G-6-PD deficiency. *Med J Aust* 1994; 161: 226–7.

Effects on wound healing. For comment on the adverse effects of hypochlorite solutions on wound healing, see Disinfection: Wounds under Uses and Administration above.

Toxicity from mixing cleaning agents. Mixing the household cleaning agents bleach (5.25% sodium hypochlorite solution) and 4% phosphoric acid (p. 2589.1) causes chlorine gas and water to be released. The chlorine in turn reacts with the water to form hydrochloric and hypochlorous acids. There have been case reports[1] of patients and hospital staff who have been accidentally exposed to chlorine gas as a result of mixing of these two cleaning agents. They had temporary illness and symptoms typical of chlorine toxicity; irritation of the eyes, nose and throat, headache, dizziness, nausea, cough, and chest pain or tightness. One patient had an acute exacerbation of asthma.

Tosylchloramide sodium gas is produced when common household cleaning agents containing sodium hypochlorite and ammonia (p. 2441.2) are mixed together. On inhalation the water in the respiratory tract reacts with the tosylchloramide sodium gas to release ammonia, hydrochloric acid and oxygen free radicals. Many case reports have described the symptoms resulting from inhalation of these gases. A 12-month review[2] of 216 patients who reported to a regional poison information centre after exposure to tosylchloramide sodium gas as a result of mixing cleaning products found that only 1 patient, with a pre-existing respiratory-tract infection, required hospital admission for ongoing respiratory distress. The most frequent symptoms were cough and shortness of breath and other symptoms experienced were those commonly associated with exposure to chlorine gas (p. 1746.3). Most (200) of the patients' symptoms resolved within 6 hours and 145 patients were treated at home, while 71 were referred for further medical care. Oxygen was given to 62 patients, bronchodilators to 9 patients and 3 patients received corticosteroids. Similar symptoms and findings were reported[3] when 2 groups of 36 soldiers were exposed to tosylchloramide sodium gas as a result of mixing sodium hypochlorite and ammonia containing cleaning agents. Only 2 soldiers required hospital admission for persistent respiratory symptoms, with one of them requiring a few days of treatment in intensive care. Another case report[4] described a previously healthy 53-year-old woman who had shortness of breath progressing to pneumonitis and required emergency tracheostomy after a similar exposure to tosylchloramide sodium gas.

1. CDC. Epidemiologic notes and reports: chlorine gas toxicity from mixture of bleach with other cleaning products—California. *MMWR* 1991; 40: 619–21, 627–9. Corrections. *ibid.*; 646, 819.
2. Mvos R, *et al.* Home exposures to chlorine/chloramine gas: review of 216 cases. *South Med J* 1993; 86: 654–7.
3. Pascurzi TA, Storrow AB. Mass casualties from acute inhalation of chloramine gas. *Mil Med* 1998; 163: 102–4.
4. Tanen DA, *et al.* Severe lung injury after exposure to chloramine gas from household cleaners. *N Engl J Med* 1999; 341: 848–9.

Toxicity during root canal irrigation. A review of case reports[1] where sodium hypochlorite had been inadvertently injected into the periapical tissues during root canal irrigation reported that most patients had immediate severe pain and swelling of the neighbouring soft tissue, which could possibly spread over the injured side of the face, upper lip and infra-orbital region. Other symptoms included bleeding from the root canal, interstitial bleeding with haemorrhage of the skin and mucosa, a chlorine taste, irritation of the throat, and reversible anaesthesia or paraesthesia.

1. Hülsmann M, Hahn W. Complications during root canal irrigation—literature review and case reports. *Int Endod J* 2000; 33: 186–93.

Treatment of Adverse Effects

If sodium hypochlorite solution is ingested symptomatic care, including dilution with water, milk, or other demulcents should be given; opinion over the use of antacids is divided. If spilled on skin or eyes, washing with copious amounts of water is recommended.

Poisoning. A patient who accidentally received an intravenous infusion of 150 mL of a 1% solution of sodium hypochlorite had a slow heart rate, mild hypotension, and increased respiratory rate. The slow heart rate persisted for 3 days but other parameters returned to normal after symptomatic treatment.[1]

1. Marroni M, Menichetti F. Accidental intravenous infusion of sodium hypochlorite. *DICP Ann Pharmacother* 1991; 25: 1008–9.

Precautions

Topically applied hypochlorites may dissolve blood clots and cause bleeding.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Milton; *Belg.*: Dakin-cooper; *Canad.*: Advance 12A; Ali-Flex; Basic 12†; Chemspec Dakin's Solution; Exsept; Hygeol†; *Fr.*: Dakin; *Israel*: Chlorasol; *Ital.*: Amukine Med; Milton; *UK*: Milton; *USA*: Hysept.

Multi-ingredient Preparations. *Fr.*: Amukine; *Gr.*: Amuchina; *Switz.*: Amukina.

Pharmacopoeial Preparations

BP 2014: Dilute Sodium Hypochlorite Solution; Strong Sodium Hypochlorite Solution;

USP 36: Sodium Hypochlorite Solution; Sodium Hypochlorite Topical Solution.

Sodium Nitrate

E251; Natril Nitras; Natrium Nitricum; Nitrato sódico; Sodu azotan; Нитрат Натрия.

$NaNO_3$=84.99

CAS — 7631-99-4.

UNII — 8M4L3H2ZVZ

NOTE. Crude sodium nitrate is known as Chile Saltpetre (Nitrato de Chile; Nitro de Chile; Salitre Chileno).

Profile

Sodium nitrate has similar actions to potassium nitrate (p. 1766.2) and is used as a preservative in foods, particularly in meat products.

Crude sodium nitrate is used as a fertiliser.

Handling. Sodium nitrate has been used for the illicit preparation of explosives or fireworks; care is required with its supply.

Poisoning. Cyanosis and methaemoglobinaemia has been reported[1] in 3 patients after eating sausages that had been preserved mistakenly with a mixture of sodium nitrate

and sodium nitrite rather than with potassium nitrate (saltpetre). The name saltpetre is used as a generic term for a number of potassium- or sodium-based preservatives used in food manufacture.

1. Kennedy N, *et al.* Faulty sausage production causing methaemoglobinaemia. *Arch Dis Child* 1997; 76: 367–8.

Preparations

Proprietary Preparations (details are given in Volume B)

Homoeopathic Preparations. *Fr.*: Aesculus Complexe No 103; Mercurius Solubilis Complexe No 39; *Ger.*: Rheuma-Pasc.

Sodium Perborate Monohydrate *(USAN)*

Натрия Пербората Моногидрат.

$NaBO_3H_2O$=99.81

CAS — 7632-04-4 (anhydrous sodium perborate); 10332-33-9 (sodium perborate monohydrate).

ATC — A01AB19.

ATC Vet — QA01AB19.

UNII — Y9UKD0XE6F.

Sodium Perborate

Natrii Perboras; Natrio perboratas; Natriumperboraatti; Natriumperborat; Nátrium-perborát; Perborato sódico; Perboritan sodný; Sod. Perbor.; Sodium, perborate de; Sodium Perborate Tetrahydrate; Натрия Пербората.

$NaBO_3.4H_2O$=153.9

CAS — 10042-94-1.

ATC — A01AB19.

ATC Vet — QA01AB19.

UNII — Y52BK1W96C.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Sodium Perborate, Hydrated; Sodium Perborate BP 2014). Colourless prismatic crystals or a white or almost white powder, stable in crystalline form. Sparingly soluble in water, with slow decomposition. It dissolves in dilute mineral acids. Store in airtight containers.

Uses and Administration

Sodium perborate is a mild disinfectant and deodorant. It readily releases oxygen in contact with oxidisable matter and has been used in aqueous solutions for purposes similar to weak solutions of hydrogen peroxide.

Sodium perborate is used for tooth whitening and has also been used, with calcium carbonate, as a toothpowder. A freshly prepared solution is used as a mouthwash.

The monohydrate is used similarly.

Adverse Effects

Frequent use of toothpowders containing sodium perborate may cause blistering and oedema. Hypertrophy of the papillae of the tongue has also been reported. The effects of swallowed sodium perborate are similar to those of boric acid (p. 2460.1).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Hifamonil; *Canad.*: Amosan; *Fr.*: Nettoyant Essilor†; *India*: Fittydent; Steradent; *Irl.*: Bocasan†; *Neth.*: Bocasan†; *USA*: Amosan.

Multi-ingredient Preparations. *Austral.*: Amosan†; *Braz.*: Anginotricin; Malvatricin Branqueador†; Oticerim; *Fr.*: Bactident†; Hydralin Classic; *Hong Kong*: Hydralin; *Spain*: Lema C; *USA*: Trichotine; *Venez.*: Novafix.

Sodium Percarbonate

Percarbonato sódico; Sodium Carbonate Peroxide; Надуглекислый Натрий; Перкарбонат Натрия.

$Na_2CO_3.1\frac{1}{2}H_2O_2$=157.0

CAS — 15630-89-4.

UNII — Z7G82NV92P.

Profile

Sodium percarbonate has similar uses to sodium perborate (above).

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Ascoxal†; *Mex.*: Ascoxal†.

Sorbates

Sorbatos; Сорбаты.

Sorbic Acid

Acide sorbique; Acidum sorbicum; E200; Kwas sorbowy; Kyselina sorbová; Sórbico, ácido; Sorbiinihappo; Sorbinsäure; Sorbinsyra; Sorbo rūgštis; Szorbinsav; Сорбиновая Кислота.

(*E,E*)-Hexa-2,4-dienoic acid.

$C_6H_8O_2$=112.1

CAS — 22500-92-1.

UNII — X045WJ989B.

Pharmacopoeias. In *Chin.* and *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Sorbic Acid). A white or almost white, crystalline powder. Slightly soluble in water; freely soluble in alcohol. Protect from light.

USNF 31: (Sorbic Acid). A free-flowing white crystalline powder with a characteristic odour. Soluble 1 in 1000 of water, 1 in 10 of alcohol, 1 in 8 of dehydrated alcohol, 1 in 15 of chloroform, 1 in 30 of ether, 1 in 8 of methyl alcohol, and 1 in 19 of propylene glycol. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Incompatibility. The incompatibility of sorbates is discussed under Potassium Sorbate, below.

Potassium Sorbate

E202; Kalii Sorbas; Kalio sorbatas; Kaliumsorbaatti; Kalium-sorbat; Kalium-sorbát; Kálium-szorbát; Potassium, sorbate de; Sorbato potásico; Сорбат Калия.

Potassium (*E,E*)-hexa-2,4-dienoate.

$C_6H_7KO_2$=150.2

CAS — 590-00-1; 24634-61-5.

UNII — 1VPU26JZZ4.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Potassium Sorbate). White or almost white granules or powder. Very soluble in water; slightly soluble in alcohol. Protect from light.

USNF 31: (Potassium Sorbate). White crystals or powder with a characteristic odour. Soluble 1 in 4.5 of water, 1 in 35 of alcohol, and 1 in more than 1000 of chloroform and of ether. Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Incompatibility. Sorbic acid can be inactivated by oxidation and to some extent by nonionic surfactants and plastics. Activity of the sorbates may be reduced by increases in pH.[1]

1. Cook W, *et al.* Sorbic acid. In: Rowe RC, *et al.*, eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press and the American Pharmaceutical Association,2009: 672–5.

Uses

Potassium sorbate and sorbic acid possess antifungal, and to a lesser extent antibacterial, activity. They are relatively ineffective above a pH of about 6. They are used as preservatives in pharmaceutical preparations in concentrations of up to 0.2%, in enteral formulas, foods, and in cosmetic preparations.

Adverse Effects and Precautions

The sorbates can be irritant and have caused contact dermatitis.

Hypersensitivity. References to allergic-type skin reactions[1] and non-allergic irritant-type reactions[2,3] with potassium sorbate or sorbic acid.

1. Saihan EM, Harman RRM. Contact sensitivity to sorbic acid in 'Unguentum Merck'. *Br J Dermatol* 1978; 99: 583–4.
2. Soschin D, Leyden JJ. Sorbic acid-induced erythema and edema. *J Am Acad Dermatol* 1986; 14: 234–41.
3. Fisher AA. Erythema limited to the face due to sorbic acid. *Cutis* 1987; 40: 395–7.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Caprilate†; *Ger.*: Saseem; *Ital.*: Evasen Discheti; Evasen Liquido; *Mex.*: Adapettes; *UK*: Feminesse; Relaxit; *USA*: Clear Eyes Contact Lens Relief; *Venez.*: Saxacid.

Sulfites and Sulfur Dioxide

Sulfitos y dióxido de azufre.

Potassium Bisulfite

Bisulfito potásico; E228; Potassium Bisulphite; Potassium Hydrogen Sulphite; Бисульфит Калия; Гидросульфит Калия.

$KHSO_3$=120.2

CAS — 7773-03-7.

UNII — QJK5LO891P.

Potassium Metabisulfite

Dipotassium Pyrosulphite; Disiřičitan draselný; E224; Kalii Disulfis; Kalii metabisulfis; Kalio metabisulfitas; Kaliummetabisulfiitti; Kaliummetabisulfit; Metabisulfito potásico; Potassium, métabisulfite de; Potassium Metabisulphite; Potassium Pyrosulphite; Potasu pirosiarczyn; Пиросульфит Калия.

$K_2S_2O_5$=222.3

CAS — 16731-55-8.

UNII — 65OE787Q7W.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF.*

Ph. Eur. 8: (Potassium Metabisulfite). A white or almost white powder or colourless crystals. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.0 to 4.5. Store in airtight containers. Protect from light.

USNF 31: (Potassium Metabisulfite). White or colourless, free-flowing crystals, crystalline powder, or granules, usually with an odour of sulfur dioxide. Gradually oxidises in air to the sulfate. Soluble in water; insoluble in alcohol. Its solutions are acid to litmus. Store in well-filled airtight containers at a temperature not exceeding 40 degrees.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, p. 1771.1.

Sodium Bisulfite

Bisulfito sódico; E222; Sodium Bisulphite; Sodium Hydrogen Sulphite; Гидросульфит Натрия.

$NaHSO_3$=104.1

CAS — 7631-90-5.

UNII — TZX5469Z6I.

Pharmacopoeias. In *Chin.* and *Jpn*, described in both a consisting of a mixture of sodium bisulfite and sodium metabisulfite.

Sodium Metabisulfite

Disiřičitan sodný; Disodium Pyrosulphite; E223; Metabisulfito sódico; Natrii Disulfis; Natrii Metabisulfis; Natrii Pyrosulfis; Natrio metabisulfitas; Nátrium-diszulfit; Natriummetabisulfiitti; Natriummetabisulfit; Sodium Disulphite; Sodium, métabisulfite de; Sodium Metabisulphite; Sodium Pyrosulphite; Sodu pirosiarczyn; Пиросульфит Натрия.

$Na_2S_2O_5$=190.1

CAS — 7681-57-4.

UNII — 4VON5FNS3C.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Ph. Eur. 8: (Sodium Metabisulfite). Colourless crystals or a white or almost white crystalline powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 3.5 to 5.0. Protect from light.

USNF 31: (Sodium Metabisulfite). White crystals or a white to yellowish crystalline powder with an odour of sulfur dioxide. Freely soluble in water and in glycerol; slightly soluble in alcohol. Store in well-filled airtight containers at a temperature not exceeding 40 degrees.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, p. 1771.1.

Sodium Sulfite

Anhydrous Sodium Sulphite; E221; Exsiccated Sodium Sulphite; Natrii Sulfis; Natrii sulfis anhydricus; Natrii Sulfis Siccatus; Natrii Sulphis; Natrio sulfitas, bevandenis; Natriumsulfiitti, vedetön; Natriumsulfit, vattenfritt; Siřičitan sodný; Sodium (sulfite de) anhydre; Sodium Sulphite; Sodu siarczyn; Sulfito sódico; Vízmentes nátrium-szulfit; Сульфит Натрия.

Na_2SO_3=126.0

CAS — 7757-83-7.

UNII — VTK01UQK3G.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), and *Jpn.* Also in *USNF.*

Eur. also includes the heptahydrate.

Ph. Eur. 8: (Sodium Sulfite, Anhydrous; Natri Sulfis Anhydricus). A white or almost white powder. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Sodium Sulphite Heptahydrate; Natrii Sulfis Heptahydricus). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol.

USNF 31: (Sodium Sulfite). Colourless crystals. Freely soluble in water; very slightly soluble in alcohol. Store in airtight containers.

Incompatibility and stability. The incompatibility and stability of sulfites are discussed under Sulfur Dioxide, below.

Sulfur Dioxide

Anhídrido sulfuroso; Dióxido de azufre; E220; Kükürt Dioksit; Siarki dwutlenek; Sulphur Dioxide; Диоксид Серы.

SO_2=64.06

CAS — 7446-09-5.

UNII — 0UZA3422Q4.

Pharmacopoeias. In *USNF*.

USNF 31: (Sulfur Dioxide). A colourless non-flammable gas with a strong suffocating odour characteristic of burning sulfur. It condenses readily under pressure to a colourless liquid that boils at -10 degrees and has a wt per mL of about 1.5 g. Soluble 36 in 1 of water and 114 in 1 of alcohol by vol. at 20 degrees and standard pressure. Soluble in chloroform and in ether. Store in cylinders. It is usually packaged under pressure in liquid form.

Incompatibility and stability. Sulfite antoxidants can react with and inactivate sympathomimetics such as adrenaline.[1] Measures need to be taken to prevent such a reaction if sulfites have to be used. Cisplatin is another compound that can be inactivated.[2] Phenylmercuric nitrate may be inactivated or its activity enhanced.[3,4] Sulfites are reported to react with chloramphenicol.[1] Hydrogen peroxide generation has been reported on exposure to light of amino acid solutions containing sulfites.[5] When used in foods there can be a noticeable taste and a reduction in thiamine content.[6] Stability is affected by air and moisture, and there is decomposition at very low pH.[7] There can be adsorption on to rubber closures.[8]

1. Higuchi T, Schroeter LC. Reactivity of bisulfite with a number of pharmaceuticals. *J Am Pharm Assoc (Sci)* 1959; 48: 535–40.
2. Garren KW, Repta AJ. Incompatibility of cisplatin and Reglan Injectable. *Int J Pharmaceutics* 1985; 24: 91–9.
3. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; 24 (suppl): 84P–89P.
4. Collins AJ, *et al.* Incompatibility of phenylmercuric acetate with sodium metabisulphite in eye drop formulations. *J Pharm Pharmacol* 1985; 37 (suppl): 123P.
5. Brawley V, *et al.* Effect of sodium metabisulfite on hydrogen peroxide production in light-exposed pediatric parenteral amino acid solutions. *Am J Health-Syst Pharm* 1998; 55: 1288–92.
6. FAO/WHO. Evaluation of the toxicity of a number of antimicrobials and antioxidants: sixth report of the joint FAO/WHO expert committee on food additives. *WHO Tech Rep Ser 228* 1962. Also available at: http://libdoc.who.int/trs/WHO_TRS_228.pdf (accessed 25/06/10)
7. Kabir MA, Reo JP. Sodium metabisulfite. In: Rowe RC, *et al.* eds. *Handbook of pharmaceutical excipients.* 6th ed. London and Chicago: The Pharmaceutical Press, and the American Pharmaceutical Association2009: 654–6.
8. Schroeter LC. Sulfurous acid salts as pharmaceutical antioxidants. *J Pharm Sci* 1961; 50: 891–901.

Uses

Sulfur dioxide and the sulfites that produce sulfur dioxide and sulfurous acid are strong reducing agents and are used as antoxidants. Concentrations of the sulfites in pharmaceutical preparations have ranged from 0.01 to 1.0%. At higher concentrations and preferably at an acid pH sulfur dioxide and the sulfites have antimicrobial activity.

Sulfur dioxide and the sulfites are used in the food industry as antoxidants, antimicrobial preservatives, and anti-browning agents. They are used in wine making where tabletted sodium metabisulfite is commonly known as Campden Tablets. Concentrations of sulfites above 500 ppm impart a noticeable unpleasant taste to preparations. There is concern over the risk of severe allergic reactions arising from the use of sulfites in foods (see Hypersensitivity, below).

Adverse Effects and Precautions

Gastric irritation due to liberation of sulfurous acid can follow ingestion of sodium metabisulfite and other sulfites. Large doses of sulfites may cause gastrointestinal upsets, respiratory or circulatory failure, and CNS disturbances.

Concentrated solutions of salts of sulfurous acid are irritant to skin and mucous membranes.

Sulfur dioxide is highly irritant to the eyes, skin, and mucous membranes. Inhalation results in irritation of the respiratory tract which may lead to bronchoconstriction and pulmonary oedema; very high concentrations may cause respiratory arrest and asphyxia. Contact with liquid sulfur dioxide results in acid burns.

Allergic reactions including anaphylaxis and deaths have been reported.

Hypersensitivity. Hypersensitivity reactions including bronchospasm, anaphylaxis; and some deaths have occurred in subjects, especially those with a history of asthma or atopic allergy, exposed to sulfites used as preservatives in foods.[1] These reactions have led to restrictions by the FDA on such use.[2] There have been case reports of reactions to sulfites in medicines;[3-9] such reports are considered to be few in number and the FDA has not extended the restriction on sulfites in foods to apply to their use in drugs since it was felt that in certain cases there was no suitable alternative to a sulfite.[2] It was even accepted that adrenaline recommended for use in treating allergic reactions could itself contain sulfite and that its presence should not preclude use of the adrenaline preparation even in sulfite-sensitive patients.[2]

1. Anonymous. Sulfites in drugs and food. *Med Lett Drugs Ther* 1986; 28: 74–5.
2. Anonymous. Warning for prescription drugs containing sulfites. *FDA Drug Bull* 1987; 17: 2–3.
3. Baker GJ, *et al.* Bronchospasm induced by metabisulphite-containing foods and drugs. *Med J Aust* 1981; ii: 614–17.
4. Twarog FJ, Leung DYM. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA* 1982; 248: 2030–1.
5. Koepke JW, *et al.* Dose-dependent bronchospasm from sulfites in isoetharine. *JAMA* 1984; 251: 2982–3.
6. Mikolich DJ, McCloskey WW. Suspected gentamicin allergy could be sulfite sensitivity. *Clin Pharm* 1988; 7: 269.
7. Deziel-Evans LM, Hussey WC. Possible sulfite sensitivity with gentamicin infusion. *DICP Ann Pharmacother* 1989; 23: 1032–3.
8. Campbell JR, *et al.* Allergic response to metabisulfite in lidocaine anesthetic solution. *Anesth Prog* 2001; 48: 21–6.
9. Riemersma WA, *et al.* Type IV hypersensitivity to sodium metabisulfite in local anaesthetic. *Contact Dermatitis* 2004; 51: 148.

Pharmacokinetics

Sulfites and metabisulfites are oxidised in the body to sulfate and excreted in the urine. Any sulfurous acid or sulfur dioxide is also converted to sulfate.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Thai.*: Peritoneal Lactate†.

Tar Acids

Alquitrán, ácidos de.

Description. Tar acids are phenolic substances derived from the distillation of coal tar or petroleum fractions. The lowest boiling fraction of coal tar, distilling at 188 degrees to 205 degrees, consists of mixed cresol isomers. The middle fraction, known as 'cresylic acids', distils at 205 degrees to 230 degrees and consists of cresols and xylenols. The 'high-boiling tar acids', distilling at 230 degrees to 290 degrees, consist mainly of alkyl homologues of phenol, with naphthalenes and other hydrocarbons. Cresol is described on p. 1749.1.

- **Black Fluids** are homogeneous solutions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons and with a suitable emulsifying agent.
- **White Fluids** are finely dispersed emulsions of coal-tar acids, or similar acids derived from petroleum, or any mixture of these, with or without hydrocarbons.
- **Modified Black Fluids** and **Modified White Fluids** may contain, as an addition, any other active ingredients, but if these are used, the type and amount must be disclosed, if required.

Uses

Tar acids are the phenolic components of coal tar and are used in the preparation of a range of fluids of varied activity used for household and general disinfection purposes.

Hydrocarbons are often used to enhance the activity of the tar acids in disinfectant fluids; they also help to reduce crystallisation of phenols.

Adverse Effects and Treatment

As for Phenol, p. 1764.2.

Tar acids are generally very irritant and corrosive to the skin, even when diluted to concentrations used for disinfection.

Poisoning. A report of fatal self-poisoning in a 59-year-old man after the ingestion of about 250 mL of a xylenol-containing disinfectant (*Stericol Hospital Disinfectant*).[1]

1. Watson ID, *et al.* Fatal xylenol self-poisoning. *Postgrad Med J* 1986; 62: 411–12.

Tertiary Butylhydroquinone

Butilhidroquinona terciaria; TBHQ; Третичного бутилгидрохинона.

2-tert-butylhydroquinone.

$C_{10}H_{14}O_2$=166.2

CAS — 1948-33-0.

UNII — C126749428.

Profile

Tertiary butylhydroquinone is an antoxidant preservative used in foods. It has some antimicrobial activity.

Tetrabromocresol

3,4,5,6-Тетрабром-о-крезол.

3,4,5,6-Tetrabromo-o-cresol.

$C_7H_4Br_4O$=423.7

CAS — 576-55-6.

Profile

Tetrabromocresol is a brominated phenolic antiseptic. It has been used for hand disinfection and is applied topically in preparations for the treatment of fungal infections of the skin and bromhidrosis.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Austral.*: Pedoz.

Tetraglycine Hydroperiodide

Tetraglicina, hidroperioduro de; Гидропериодид Тетраглицина.

$C_{16}H_{42}I_7N_9O_{16}$=1490.9

CAS — 7097-60-1.

Profile

Tetraglycine hydroperiodide is an iodine-based disinfectant that is used in the emergency treatment of drinking water (p. 1731.3).

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *UK*: Potable Aqua; *USA*: Potable Aqua.

Thiomersal (BAN, rINN)

Mercurothiolate; Mercurothiolate Sodique; Sodium Ethyl Mercurithiosalicylate; Thimerosal; Thiomersalate; Thiomersalum; Tiomersaall; Tiomersal; Tiomersalis; Tiomerzál; Тиомерсал.

Sodium (2-carboxyphenylthio)ethylmercury.

$C_9H_9HgNaO_2S$=404.8

CAS — 54-64-8.

ATC — D08AK06.

ATC Vet — QD08AK06.

UNII — 2225P13MOV.

Pharmacopoeias. In *Eur.* (see p. vii) and *US*.

Ph. Eur. 8: (Thiomersal). A white or almost white crystalline powder. Freely soluble in water; sparingly soluble or soluble in alcohol; practically insoluble in dichloromethane. A 0.8% solution in water has a pH of 6.0 to 8.0. Protect from light.

USP 36: (Thimerosal). A light cream-coloured crystalline powder with a slight characteristic odour. Soluble 1 in 1 of water and 1 in 12 of alcohol; practically insoluble in ether. A 1% solution in water has a pH of about 6.7. Store in airtight containers. Protect from light.

Incompatibility. Thiomersal is incompatible with acids, metal ions, and iodine. It forms precipitates with many alkaloids. The rate of oxidation of thiomersal in solution is greatly increased by traces of copper ions. In slightly acid solution thiomersal may be precipitated as the corresponding acid which undergoes slow decomposition with the formation of insoluble products. The activity of thiomersal may also be reduced by boric acid, edetic acid, or sodium thiosulfate or by the presence of blood or organic matter. Thiomersal may be adsorbed by plastic or rubber packaging materials.

References.

1. Richards RME, Reary JME. Changes in antibacterial activity of thiomersal and PMN on autoclaving with certain adjuvants. *J Pharm Pharmacol* 1972; 24 (suppl): 84P–89P.
2. Reader MJ. Influence of isotonic agents on the stability of thimerosal in ophthalmic formulations. *J Pharm Sci* 1984; 73: 840–1.
3. Morton DJ. EDTA reduces antimicrobial efficacy of thiomersal. *Int J Pharmaceutics* 1985; 23: 357–8.

Uses and Administration

Thiomersal is a bacteriostatic and fungistatic mercurial antiseptic that has been applied topically usually in a concentration of 0.1%. Its antibacterial action results from the release of ethylmercury after breakdown to thiosalicylate and ethylmercury.

Thiomersal, 0.001 to 0.01%, is used as a preservative in biological and pharmaceutical products. It has also been used to preserve solutions used in the care of contact lenses (p. 1730.2).

Adverse Effects, Treatment, and Precautions

As for Mercury, p. 2556.1.

Hypersensitivity reactions occasionally occur. Allergic conjunctivitis has been reported.

General references.

1. Risher JF, *et al.* Organic mercury compounds: human exposure and its relevance to public health. *Toxicol Ind Health* 2002; 18: 109–60.

Hypersensitivity. Both delayed (allergic contact) and immediate (including anaphylaxis and immune complex mediated disorders) hypersensitivity reactions have been associated with thiomersal.[1] The frequency of positive patch tests varies, with the National Advisory Committee on Immunization in Canada reporting[1] an average incidence of 16 to 18% and a centre in the USA an incidence of 8.7%.[2] Most reactions are local and mild,[1,3] involving application sites or blepharoconjunctivitis from ocular preparations,[3] although some people may get a delayed generalised dermatitis that can be long lasting, or have exacerbation of an existing skin condition.[1] There has also been a report of acute laryngeal obstruction in a patient previously sensitised to the substance who used a throat spray preserved with thiomersal.[4] A case of occupational allergic contact dermatitis has been reported in a nurse as a result of contact with thiomersal as a preservative in childhood vaccines.[5] A generalised maculopapular eruption from an influenza vaccine containing thiomersal has also been reported.[6] The main source of sensitisation is thought to be thiomersal-preserved vaccines. Most people with patch tests positive to thiomersal are able to tolerate thiomersal-containing vaccines, although some individuals may have long-lasting cutaneous reactions.[1] If there is a definite history of anaphylaxis, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis to thiomersal in any product, vaccines containing thiomersal should not be given. However, while such reactions have not been shown to occur as a result of thiomersal in vaccines, they remain a theoretical risk.[1]

1. National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *Can Commun Dis Rep* 2007; 33 (ACS-6): 1–13. Also available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-06.pdf (accessed 29/03/10)
2. Suneja T, Belsito DV. Thimerosal in the detection of clinically relevant allergic contact reactions. *J Am Acad Dermatol* 2001; 45: 23–7.
3. Wilson LA, *et al.* Delayed hypersensitivity to thiomersal in soft contact lens wearers. *Ophthalmology* 1981; 88: 804–9.
4. Maibach H. Acute laryngeal obstruction presumed secondary to thiomersal (merthiolate) delayed hypersensitivity. *Contact Dermatitis* 1975; 1: 221–2.
5. Klec-Swierczynska M, *et al.* Occupational allergic contact dermatitis due to thimerosal. *Contact Dermatitis* 2003; 48: 337–8.
6. Lee-Wong M, *et al.* A generalized reaction to thimerosal from an influenza vaccine. *Ann Allergy Asthma Immunol* 2005; 94: 90–4.

Poisoning. Serious adverse effects have followed parenteral and topical use of thiomersal.

Six poisonings (5 fatal) resulted from the use of 1000 times the normal concentration of thiomersal in a preparation of chloramphenicol for intramuscular injection.[1] There has also been a case report[2] of mercury poisoning associated with the intravenous use of high-dose hepatitis B immunoglobulin, preserved with thiomersal, after liver transplantation. Initial symptoms were paranoia, which rapidly progressed to severe dysarthria, static tremor, chorea, and decreased motor strength, as well as haemorrhagic gastritis. The patient responded well to chelation therapy.

Thiomersal used in topical antiseptic preparations was found to be toxic to epidermal cells.[3] After the death of 10 of 13 children as a result of treatment of omphaloceles (umbilical hernia) with a tincture of thiomersal, it was recommended that organic mercurial disinfectants be heavily restricted or withdrawn from hospital use as absorption occurred readily through intact membranes.[4]

A 44 year-old man who drank 83 mg/kg of a thiomersal-containing solution in an attempted suicide, spontaneously vomited after 15 minutes.[5] On admission to hospital a gastric lavage was performed and chelating drugs given. Despite this he developed gastritis, renal failure, dermatitis, gingivitis, delirium, polyneuropathy, respiratory failure, and coma. The patient was treated symptomatically, and 148 days after ingestion had recovered fully, except for sensory defects in two toes.

1. Axton JBM. Six cases of poisoning after a parenteral organic mercurial compound (Merthiolate). *Postgrad Med J* 1972; 48: 417–21.
2. Lowell JA, *et al.* Mercury poisoning associated with high-dose hepatitis-B immune globulin administration after liver transplantation for chronic hepatitis B. *Liver Transpl Surg* 1996; 2: 475–8.
3. Anonymous. Topical antiseptics and antibiotics: organic mercurials. *Med Lett Drugs Ther* 1977; 19: 83.
4. Fagan DG, *et al.* Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic. *Arch Dis Child* 1977; 52: 962–4.
5. Pfab R, *et al.* Clinical course of severe poisoning with thiomersal. *J Toxicol Clin Toxicol* 1996; 34: 453–60.

Vaccines. The use of thiomersal as a preservative in vaccines and its role as a possible cause of autism and neurodevelopmental disorders has been a controversial topic since 1999[1] when the regulatory authorities in both Europe[2] and the USA[3] issued statements recommending that the use of thiomersal in vaccines be phased out. This was based on the fact that the cumulative amount of mercury in the infant immunisation schedule potentially exceeds the recommended maximum level set by the US government for methyl mercury. More recently, however, studies[4] have indicated a lack of association between thiomersal-containing vaccines and neurodevelopmental disorders such as autism and speech disorders. These findings were supported by the fact that thiomersal is metabolised to ethylmercury, which has substantially different pharmacokinetics to methylmercury. Ethylmercury is more rapidly excreted and does not accumulate in the body. The EMEA has issued a further statement[5] in which it confirmed that thiomersal could be used as a preservative when no alternative was available, subject to certain labelling requirements regarding hypersensitivity. The UK CSM,[6] the US FDA,[7] and Canada's Advisory Committee on Immunization[8] have similarly concluded that there is no evidence of neurological adverse effects caused by the small amounts of thiomersal present in some vaccines; despite this, all endorse the view that the use of vaccines without thiomersal would be a prudent precautionary measure. WHO states[9,10] that there is no compelling scientific evidence of safety problems and advises that thiomersal-containing vaccines may continue to be used for global immunisation programmes because the benefit outweighs any theoretical risk of toxicity.

1. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Safety* 2005; 28: 89–101.
2. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal containing medicinal products (July 1999). EMEA publication no. 20962/99. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/2096299EN.pdf (accessed 01/03/10)
3. American Academy of Pediatrics, United States Public Health Service. Thimerosal in vaccines: a joint statement of the American Academy of Pediatrics and the Public Health Service. *MMWR* 1999; 48: 563–5.
4. Parker SK, *et al.* Thimerosal-containing vaccines and autistic spectrum disorder: a critical review of published original data. *Pediatrics* 2004; 114: 793–804.
5. European Agency for the Evaluation of Medicinal Products (EMEA). EMEA public statement on thiomersal in vaccines for human use—recent evidence supports safety of thiomersal-containing vaccines (March 2004). EMEA publication no. 1194/04. Full version: http://www.emea.europa.eu/pdfs/human/press/pus/119404en.pdf (accessed 01/03/10)
6. CSM/MHRA. Safety of thiomersal-containing vaccines. *Current Problems* 2003; 29: 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007450&RevisionSelectionMethod=LatestReleased (accessed 01/03/10)
7. FDA. Thimerosal in vaccines (updated February 2009). Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/ucm096228 (accessed 01/03/10)
8. National Advisory Committee on Immunization (NACI). Thimerosal: updated statement. *Can Commun Dis Rep* 2007; 33 (ACS-6): 1–13. Also available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07pdf/acs33-06.pdf (accessed 29/03/10)
9. WHO. Guidelines on regulatory expectations related to the elimination, reduction or replacement of thiomersal in vaccines. *WHO Tech Rep Ser 926* 2004. Available at: http://www.who.int/biologicals/publications/trs/areas/vaccines/thiomersal/Annex%204%20(95-102)TRS926thiomersal.pdf (accessed 01/03/10)
10. WHO. Statement on thiomersal (issued July 2006). Available at: http://www.who.int/vaccine_safety/topics/thiomersal/statement_jul2006/en/index.htm (accessed 01/03/10)

Interactions

Tetracyclines. Nine patients using a contact lens solution containing 0.004% thiomersal developed varying degrees of ocular irritation after taking oral *tetracyclines* concurrently. Exposure to either the tetracyclines or thiomersal alone did not cause the response.[1]

1. Crook TG, Freeman JJ. Reactions induced by the concurrent use of thimerosal and tetracycline. *Am J Optom Physiol Opt* 1983; 60: 759–61.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Lithiorsan†; Merthiolate; *Chile*: Intrasept; *Mon.*: Vitaseptol†; *S.Afr.*: Merthiolate; Thiomersalate†; *Thai.*: Merthiolate; Pyrad Thimero Sahakarn; *USA*: Aeroaid†; Mersol†; *Venez.*: Merthiolate.

Multi-ingredient Preparations. *Spain*: Proskin.

Pharmacopoeial Preparations

USP 36: Thimerosal Tincture; Thimerosal Topical Aerosol; Thimerosal Topical Solution.

Thymol

Acido Timico; Ácido tímico; Isopropylmetacresol; Thymolum; Timol; Timolis; Tymol; Tymoli; Тимол.

2-Isopropyl-5-methylphenol.

$C_{10}H_{14}O$=150.2

CAS — 89-83-8

ATC Vet — QP53AX22.

UNII — 3J50XA376E

Pharmacopoeias. In *Eur.* (see p. vii) and *Jpn.* Also in *USNF*.

Ph. Eur. 8: (Thymol). Colourless crystals. The melting range is 48 degrees to 52 degrees. Very slightly soluble in water; very soluble in alcohol; freely soluble in volatile and in fixed oils; sparingly soluble in glycerol; dissolves in dilute solutions of alkali hydroxides. Protect from light.

USNF 31: (Thymol). Colourless, often large, crystals or white crystalline powder with an aromatic thyme-like odour. The melting range is 48 degrees to 51 degrees; when melted it remains liquid at a considerably lower temperature. Soluble 1 in 1000 of water, 1 in 1 of alcohol and of chloroform, 1 in 1.5 of ether, and 1 in 2 of olive oil; soluble in glacial acetic acid and in fixed and volatile oils. Store in airtight containers. Protect from light.

Incompatibility. The antimicrobial activity of thymol is reduced by combination with protein.

Uses and Administration

Thymol is a phenolic antiseptic with antibacterial and antifungal activity. It is more powerful than phenol but its use is limited by its low solubility in water, irritancy, and susceptibility to protein.

Thymol is used chiefly as a deodorant in mouthwashes and gargles such as Compound Thymol Glycerin (BP 1988) an aqueous mixture of thymol 0.05% and glycerol 10% with colouring and flavouring, which may be used diluted with about 3 times its volume of warm water before use. Thymol has been used topically in the treatment of skin disorders and is also inhaled, with other volatile substances, for colds, coughs, and associated respiratory disorders.

Thymol 0.01% is added as an antioxidant to halothane, trichloroethylene, and tetrachloroethylene.

Thymol iodide is used in preparations for dental hygiene.

Adverse Effects, Treatment, and Precautions

As for Phenol, p. 1764.2.

When ingested, thymol is less toxic than phenol. It is irritant to the gastric mucosa. Fats and alcohol increase absorption and aggravate the toxic symptoms.

Hypersensitivity. Contact allergy to a heparinoid cream was due to an allergen formed by the reaction between thymol and the degradation products of a triazine derivative, both present as preservatives.[1]

1. Smeenk G, *et al.* Contact allergy to a reaction product in Hirudoid cream: an example of compound allergy. *Br J Dermatol* 1987; 116: 223–31.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Canad.*: Benefect†; *S.Afr.*: Listerine Cool Mint; Listerine Freshburst.

Multi-ingredient Preparations. *Arg.*: Fungicida; Inhalador Medex; Listerine Clasico; Listerine Cool Mint; Listerine Fresh Burst; Manzan; Pastillas Pagliano; Periobacter Prof Avio; Pervinox Extra Mint; Pervinox Fresh Mint; Pervinox Fruit; Vagicural; *Austral.*: SM-33; Vicks Vaporub; *Austria*: DDD†; Kinder Luuf; Luuf Balsam; Pe-Ce†; Spasmo Claim†; Thrombocid; Wick Vaporub; *Belg.*: Borostyrol; Dentophar†; Perubore†; Vicks Vaporub; *Braz.*: Angino-Rub; Cloraseptic Cutisanol; Fluomint†; Salonpas; Vick Vaporub; *Canad.*: Antiseptic Mouthwash; Carboseptol†; Cresophene; Endomethasone; Faces Antiseptic†; Lipsorex Plus; Lipsorex; Listerine Antiseptic Tartar Control; Listerine Antiseptic with Fluoride; Listerine; Original Antiseptic Mouthwash†; Thermo-Gel; Vaporizing Ointment†; *Chile*: Hansaplast Descongestionante†; Listerine; Listermint Con Fluor†; Oralfresh Citrus†; Oralfresh Clasico†; Salonpas; *China*: Kamistad (甘美达); Cz.: Pinosol†; Pinosol; Septolete; *Fin.*: Vicks Vaporub; *Fr.*: Activox; Borostyrol; Cresophene; Eucaryl; Listerine protection dents et gencives; Listerine Stay White; Nisacalm†; Pastilles Medicinales Vicks; Perubore; Valda†; Vicks Vaporub; *Ger.*: Pulmotin; Retterspitz Ausserlich; Retterspitz Quick Bronchial; Retterspitz Quick Muskel; Salviathymol N; Thrombocid; *Gr.*: EKS; Endomethasone†; Export Salonpas; Oulogram; Revigel; Santoux; Vicks Vaporub; *Hong Kong*: Gly Thymol; Glycerine Thymol Co†; Kamistad; Listerine Cool Mint; Listerine Tartar Control; Listerine Teeth and Gum Defence; Listerine; Salomethyl†; Salonpas Medicated Plaster†; *Hung.*: Diapulmon; Kinder Luuf Balsam; Pinosol; Pinosol; Pulminetta; Salonpas Liniment; Septolete; *India*: AM-PM Special; Arofil; Artrex; Cool Mint Listerine; Cureg; Dordent; Icee; Listerine; Me-Fresh Gum Paint; *Indon.*: Dactylen; Listerine Coolmint†; Listerine†; Skintex†; Vital Bar Oil; *Irl.*: Karvol; *Israel*: Cresophene†; Gargol; Karvol; Pronestin; Rectozorin; Rectozorin; *Ital.*: Eugenol-Guaiacolo Composto; Listerine Fresh Citrus; Listerine Tartar Control; Pinselina Knapp; Rinostil; *Malaysia*: Salonpas; *Mex.*: Dermacid; Listerine; *Mon.*: Glyco-Thymoline; *Neth.*: Vicks Vaporub; *NZ*: Listerine Citrus Fresh; Listerine Tartar Control†; Listerine Teeth Defence; Listerine; Vicks Vaporub; *Philipp.*: Calmoseptine; Listerine Coolmint; Listerine Fresh Citrus; Listerine Freshburst; Listerine Original; Listerine Tartar

Control; Listerine Teeth & Gum Defense; Mentopas; *Pol.*: Afronis; Bronchosol; Derhotill; Icy Rub; Pinosolt; Pulmonil; Rub-Arom; Septolete; Sonol; Wick Vaporub; *Port.*: Thrombocid; *Rus.*: Bioprost (Биопрост); Doktor Mom (Доктор Мом); Efcamon (Эфкамон); Eucasept (Эвкасепт); Inhalipt (Ингалипт); Novoinhalipt (Новоингалипт); Parodontocide (Пародонтоцид); Pinosol (Пиносол); Pinosol (Пиносол); Pinosol (Пиносол); Pinovitum (Пиновитум); Septogal (Септогал); Septolete (Септолете); Suprima-Plus (Суприма-Плюс); *S.Afr.*: Karvol†; Listerine Antiseptic; Prep†; Tartar Control Listerine†; Vicks Vaporub†; *Singapore*: Kamistad†; Karvol; Listerine Bright & Clean; Listerine Cool Citrus; Listerine Cool Mint; Listerine Fresh Burst; Listerine Tartar Control†; Listerine Teeth & Gum Defense; Listerine; *Spain*: Arkoresp†; Co Bucal; Mentobox; Piorlis†; Vicks Vaporub; *Swed.*: Vicks Vaporub; *Switz.*: Butaparin†; Denosol; Eau-de-vie de France Klosterfrau au menthol; Ederphyt†; Furodermal†; Heparinol†; Penta†; Rapura; Vicks Vaporub N; *Thal.*: Analgen; Burnol Plus; Flavinol; Kamistad†; Methyl Salicylate Cream, Compound; Pataryer; Stopain; *Turk.*: Garol; Kataljin; Mentimol; Mentolin; Oka Mentol; Otaci Meyanball; Otaci Oka Mentol; Otaci Salvia; Vicks Vaporub; *UK*: Antiseptic Mouthwash; DDD; DDD; Dragon Balm; Karvol; Listerine Antiseptic Mouthwash; No-Sor Vapour Rub; Potter's Catarrh Pastilles; *Ukr.*: Doktor Mom (Доктор Мом); Helpex Effect (Хелпекс Эффект); Kamident (Камидент); Pinosol (Пиносол)†; Pinosol (Пиносол); Pinosol (Пиносол); Pinovit (Піновіт); Rostiran (Ростиран); Septolete (Септолете); *USA*: BFI; Boil Ease; Listerine; Massengill; Vicks Menthol Cough Drops; Zonite; *Venez.*: Amicets; Lafarcaina.

Tosylchloramide Sodium *(BAN, rINN)*

Chloramidum; Chloramina; Chloramine; Chloramine T; Chloraminum; Cloramina; Kloramin; Mianin; Natrium Sulfaminochloratum; Tosilchloramido natrio druska; Tosilcloramida sódica; Tosylchloramid-Natrium; Tosylchloramid sodná sůl trihydrát; Tosylchloramide Sodique; Tosylchloramidum Natricum; Tosylchloramidum Natricum Trihydricum; Tosylkloramidnatrium; Tosyylikloramidinatrium; Тозилхлорамид Натрий.

Sodium *N*-chlorotoluene-*p*-sulphonimidate trihydrate.

$C_7H_7ClNNaO_2S,3H_2O$=281.7

CAS — 144-86-5 (tosylchloramide); 127-65-1 (tosylchloramide sodium).

ATC — D08AX04.

ATC Vet — QD08AX04.

UNII — 4IU6VSV0EI (tosylchloramide sodium); 328AS34YM6 (anhydrous tosylchloramide sodium).

NOTE. The name Chloramin has also been used for a preparation of chlorphenamine maleate (p. 620.3).

Pharmacopoeias. In *Eur.* (see p. vii) and *Viet.*

Ph. Eur. 8: (Tosylchloramide Sodium). A white or slightly yellow, crystalline powder. Freely soluble in water; soluble in alcohol. A 5% solution in water has a pH of 8.0 to 10.0. Store in airtight containers. Protect from light.

Uses and Administration

Tosylchloramide sodium is an organic chlorine-releasing compound. It has general properties similar to those of chlorine (p. 1746.2) but is more stable. It contains about 25% w/w of 'available chlorine' (see p. 1746.3). It is stable at an alkaline pH although it is much more active in acid media. It is more slowly active than hypochlorite solutions.

Tosylchloramide sodium is used for the treatment of minor wound infections and as a skin and hard surface disinfectant. It is also used for the treatment of drinking water (p. 1731.3). It was formerly used as a spermicide.

Tosylchloramide sodium B (chlorogenium; sodium *N*-chlorobenzenesulphonimidate sesquihydrate) has been used similarly to tosylchloramide sodium.

Adverse Effects and Treatment

Vomiting, cyanosis, circulatory collapse, frothing at the mouth, and respiratory failure can occur within a few minutes of tosylchloramide sodium ingestion. Fatalities have occurred. Tosylchloramide sodium in tap water has caused methaemoglobinaemia and haemolysis in patients undergoing dialysis. Bronchospasm has occurred after inhalation.

Treatment of adverse effects is similar to that for Sodium Hypochlorite, p. 1769.3.

Effects on the lungs. A study in Finland in dental staff who had reported occupational respiratory hypersensitivity between 1990 and 1998 found that 1 of 28 cases of rhinitis and 3 of 28 cases of asthma could be attributed to tosylchloramide sodium.[1] For further reference to respiratory effects associated with tosylchloramide sodium gas, see under Sodium Hypochlorite: Toxicity from mixing cleaning agents, p. 1769.2.

1. Piirilä P, *et al.* Occupational respiratory hypersensitivity in dental personnel. *Int Arch Occup Environ Health* 2002; **75**: 209–16.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Belg.*: Chloraseptine; Chlorazol; Chloronguent; Clonazone; *Fr.*: Clonazone†; Hydroclonazone; *Ger.*: Chloramin T; Clorina; Trichlorol; *Hung.*: Neomagnol; *Ital.*: Citromed Chlor; Dermedal; Euclorina; Minachlor; Steridrolo.

Triclocarban *(USAN, rINN)*

NSC-72005; TCC; Triclocarbán; Triclocarbanum; Триклокарбан; 3,4,4′-Trichlorocarbanilide.

1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea.

$C_{13}H_9Cl_3N_2O$=315.6

CAS — 101-20-2.

UNII — BGG1Y1ED0Y.

Uses and Administration

Triclocarban is an anilide antiseptic. It is bacteriostatic against Gram-positive organisms but is not effective against Gram-negative organisms. It inhibits growth of some fungi. It is used in antiperspirants and soaps for disinfection of skin and mucous membranes.

Adverse Effects and Precautions

When subjected to prolonged high temperatures triclocarban can decompose to form toxic chloroanilines, which can be absorbed through the skin and cause methaemoglobinaemia. Mild photosensitivity has been seen in patch testing.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Sodorant; Ungel; *Fr.*: Cutisan; Nobacter; Solubacter; *Gr.*: Antibacter Forte; *Hong Kong*: Solubacter†; *India*: Neko; *Ital.*: Sangen Sapone Disinfettante; *UK*: Valderma.

Multi-ingredient Preparations. *Arg.*: Sodorant; *Braz.*: Soapex; *Fr.*: Septosan†; Spray du Marcheur†; *Mex.*: Septosan; *Switz.*: Septivon.

Triclosan *(BAN, USAN, rINN)*

CH-3565; Cloxifenol; Triclosán; Triclosanum; Триклозан.

5-Chloro-2-(2,4-dichlorophenoxy)phenol; 2,4,4′-Trichloro-2′-hydroxydiphenyl ether.

$C_{12}H_7Cl_3O_2$=289.5

CAS — 3380-34-5.

ATC — D08AE04; D09AA06.

ATC Vet — QD08AE04; QD09AA06.

UNII — 4NM5039Y5X.

Pharmacopoeias. In *US.*

USP 36: (Triclosan). A fine whitish crystalline powder. M.p. about 57 degrees. Practically insoluble in water; soluble in alcohol, in acetone, and in methyl alcohol; slightly soluble in petroleum spirit. Store in airtight containers. Protect from light.

Profile

Triclosan is a chlorinated bisphenol antiseptic, effective against Gram-positive and most Gram-negative bacteria but with variable or poor activity against *Pseudomonas* spp. It is also active against fungi. It is used in soaps, creams, and solutions in concentrations of up to 2% for disinfection of the hands and wounds and for disinfection of the skin before surgery, injections, or venepuncture. It is also used in oral hygiene products and in preparations for acne. There have been isolated reports of contact dermatitis.

Consumer products. Triclosan in relatively low concentrations (typically 0.1 to 0.45%) is commonly found in soaps used in community settings, although a review[1] has concluded that such use is usually no more effective than plain soap. Furthermore, there may be a risk of developing triclosan-adapted antibacterial cross-resistance. The FDA intends to review the benefit and safety of triclosan in consumer products and will consider such data as well as reports from *animal* studies which have suggested it may also alter levels of various hormones.[2]

1. Aiello AE, *et al.* Consumer antibacterial soaps: effective or just risky? *Clin Infect Dis* 2007; **45** (suppl 2): S137–S147.
2. FDA. Triclosan Facts (issued March 2010). Available at: http://www.epa.gov/oppsrrd1/REDs/factsheets/triclosan_fs.htm (accessed 03/08/10)

MRSA control. Control of meticillin-resistant *Staphylococcus aureus* (MRSA) infection in surgical units has been achieved by procedures including handwashing and bathing with triclosan.[1-3] In the UK, guidelines on the control of MRSA recommend it as one of several alternatives for such purposes,[4] although alcohol hand rubs (also mentioned in the guidelines) are currently preferred for general hand hygiene (see p. 1732.1). However, triclosan resistance has been reported.[5-7]

1. Bartzokas CA, *et al.* Control and eradication of methicillin-resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1984; **311**: 1422–5.
2. Bartzokas CA. Eradication of resistant Staphylococcus aureus on a surgical unit. *N Engl J Med* 1985; **312**: 858–9.
3. Brady LM, *et al.* Successful control of endemic MRSA in a cardiothoracic surgical unit. *Med J Aust* 1990; **152**: 240–5.
4. Coia JE, *et al.* Joint Working Party of the British Society of Antimicrobial Chemotherapy, the Hospital Infection Society, and the Infection Control Nurses Association. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect* 2006; **63** (suppl 1): S1–S44. Also available at: http://www.his.org.uk/_db/_documents/MRSA_Guidelines_PDF.pdf (accessed 14/05/10)
5. Cookson BD, *et al.* Transferable resistance to triclosan in MRSA. *Lancet* 1991; **337**: 1548–9.
6. Sasatsu M, *et al.* Triclosan-resistant Staphylococcus aureus. *Lancet* 1993; **341**: 756. Correction. *ibid.*; **342**: 248.
7. Suller MT, Russell AD. Triclosan and antibiotic resistance in Staphylococcus aureus. *J Antimicrob Chemother* 2000; **46**: 11–18.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Daewo; Hekabetol; Xicanil Control Dermo; *Austral.*: Clean & Clear Foaming Facial Wash; Dettol Liquid Wash; Gamophen; Microshield T; Neutrogena Acne Skin Cleanser; Oxy Medicated Skin Wash†; pHisoHex Face Wash; Sapoderm; *Braz.*: Clean & Clear Sabonete Liquido Facial; Hygine; Johnson's Sabonete Liquido Anti-Septico; Soapelle; Soapex; Theracne; *Canad.*: Acnopur†; Adasept; After Sport; Anti-Bac; Anti-Bacterial Moisturizing; Anti-Microbial; Antiseptic Hand Soap; Applaud; Asept; Aspen Hand Soap; Bacti-Foam; Bacti-Stat; Bio-Safe; Biodenz†; Cherry Creme Hand Soap; Chlorosept†; Clean & Clear Foaming Facial Cleanser; Clearskin Dual Action†; Clinishield; Crown Antiseptic Hand Soap; Dermacne; Dermasept Plus†; Dial Complete; Digiclean Antibacterial; Digiclean E Hand Soap†; Digiclean Slim-Line; Eco-Clean†; Ecocare 250; Endure; Episoft; Florafree; Fresh Power Gold; Gentle Fresh Defense; Gentle Rain; Hands On Defense; HFS; Kimcare Antibacterial†; Lever; Lotion Kleen Green; Moisturizing Antibacterial Hand Cleanser; Naturals Antibacterial Liquid Soap; Noxzema Triple Clean; Perle + Antiseptic; Prime Source; Provon Medicated; Reliable Mousse Foaming Antiseptic; Signatry; Simply Botanical Sensations Soothing Skin; Skin Shield; Skinvisible; Soapy Sudz; Soft Care Antibacterial; Soft Care Cross-Contamination Control; Soft Care Foam Select; Soft Care Nutra-Germ; Softcide EC; Sport Gel†; Stoko; Summer Rain; Surgi Bac†; Sysco Antimicrobial†; Tersaseptic; Valour; West Antiseptic Soap; Winning Hands Hand Cleanser; *Zep*; *Chile*: Antiseptin; Lavasept; *Sanigermin*; *China*: Sicorten Plus (新适确得); *Fr.*: Nobacter; *Gr.*: Ampitasol; *Hong Kong*: Dettol†; Oxy Daily Wash†; *India*: Medsop; Microshield T; *Indon.*: pHisoHex Reformulated; *Israel*: Dermax; *Ital.*: Cetriderm con Triclosan†; Derman Plus†; Geroderm; Ippi Verde†; Irgaman; Lactacyd Antibatterico†; Till; *Malaysia*: A-Septic AS; *Mex.*: Axel; *NZ*: Dalacin T Prewash; Liquid Soap Pre-Op; *Philipp.*: Lipo Sol†; *S.Afr.*: Acnecleart; *Singapore*: T3 Continuous Control Wash; *Switz.*: Clinideram; Cremolan; Lipo Sol; Procoutol; *Thai.*: Virulex†; *UK*: Aquasept†; Gamophen; Oxy Facial Wash; Ster-Zac†; *USA*: AmeriWash; ASC; Ca-Rezz; Clean & Clear Foaming Facial Cleanser; Clearasil Daily Face Wash; Oxy Medicated Soap; Sarna Sensitive; Stri-Dex Antibacterial Cleansing; Stri-Dex Face Wash.

Multi-ingredient Preparations. *Arg.*: Bentophyto; Dettonjab; Emoform Total; Esmedent con Fluor; Esmedent Dientes Sensibles; Heduline; Hekabetol; Neoceuticals Gel de Limpieza Facial; Prurigel; Sebosoap; Sebulex; Xicanil Control NF Crema; Xicanil Control NF Locion; Xicanil Control NF; Xicanil Control†; *Austral.*: Clearasil Pimple Treatment Cream†; Dettol Cream; Oilatum Plus; QV Flare Up; *Braz.*: Fisohex II; Malvatricin Antiplaca†; Malvatricin Branqueador†; Malvatricin Dentes Sensiveis†; Malvatricin Plus†; Sallsoap; Soapex; Suavederm; *Canad.*: Adasept; Anti-Bacterial Deep Cleansing; Antiseptic Hand Soap; Ensuite; Inhibit; PanOxyl Clear Acne†; Solarcaine; Soothing Foot Spray; Uphold Plus; *Chile*: Ac-Sal†; Acniben Toallitas; Cariamyl; Cariamyl; Dermaliv; Fittig Desodorante; Hansaplast Antimicotico†; Hansaplast Footcare†; Normaderm Stick Secante Camufu Imperfecciones; Softcain; Solarcaine Spray Aerosol; *Cz.*: Oilatum Plus; *Fin.*: Wicnelact; *Fr.*: Clinogel†; Dermalibour; Ephydrol; Poudre du Marcheur†; Septosan†; Spray du Marcheur†; *Ger.*: DuoGalen; InfectoCortiSept; Rutisept extra; Sicorten Plus†; *Hong Kong*: Dettol†; Oilatum Plus; Sensodyne Gentle†; *Hung.*: Aurobin; *India*: Acnelak; AM-PM Junior; AM-PM Plus; AM-PM Special; Clin-3; Deosan; Kidodent; Klinit; Oilatum Plus; *Indon.*: Betiga†; Oilatum Plus†; Verile; *Irl.*: Colgate Total; Dettol†; Manusept; Oilatum Junior Flare-Up; Oilatum Plus; TCP; *Israel*: Pedisol†; *Ital.*: Aknicare Cleanser; Angstrom Viso; AZ Protezione Gengive; Colgate Total; Dopo Pik; Geroderm Zolfo; Plax; Sensigel; Sensiquell; Steril Zeta; Steril Zeta; *Malaysia*: AcneCare; Clearasil Pimple Treatment; Dettol; Oilatum Plus Antibacterial; QV Flare Up†; T3 Acne; T3 Concealer; *Mex.*: Axel; Cetaphil Antibacterial; Dermobras; Periodentyl; Periodentyl; Prespir; Sebryl Plus; Septosan; *NZ*: Clearasil; Dettol; Oilatum Plus; Solarcaine†; *Philipp.*: Oilatum Plus; Sebo Fluid†; *Pol.*: Oilatum Plus; *Port.*: Aknicare; Alkagin; Bexident; Lambda; *Rus.*: Aurobin (Ауробин); *S.Afr.*: Clearasil T†; Oilatum Plus; *Singapore*: Burnaid; Clearasil Pimple Treatment; Dettol; Oilatum Plus; QV Flare Up; T3; *Spain*: Doctodermis; Sicorten Plus†; Vaselatum; *Switz.*: Acne Creme; Acne Gel; Acne Lotion;

Antebor N†; Pixor Stick Anti-acne N; Sicorten Plus; Sulgan N; Undex†; *Thal.*: Dettol; Hand Joy; Oilatum Plus†; *Turk.*: Alkagin; *UK*: Clearasil Active Treatment Cream; Dentyl pH; Dettol; Manusept; Oilatum Plus; Oxy Clean Facial Scrub; Oxy Cleanser; Oxy Dots; Oxy Duo Pads; Sensodyne-F; Solarcaine; TCP; *Ukr.*: Aurobin (Ауробин); *USA*: Clearasil Antibacterial; Solarcaine; *Venez.*: Exfoliderm.

Troclosene *(rINNM)*

Dichloroisocyanuric Acid; Troclosène; Trocloseno; Troclosenum; Троклозен.
1,3-Dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione.
$C_3HCl_2N_3O_3$=198.0
CAS — 2782-57-2.
UNII — PHR838Y52L.

Troclosene Potassium *(USAN, rINN)*

Potassium Dichloroisocyanurate; Potassium Troclosene; Troclosène Potassique; Trocloseno de potasio; Troclosenum Kalicum; Троклозен Калий.
$C_3Cl_2KN_3O_3$=236.0
CAS — 2244-21-5.
UNII — 8A85D111P0.

Troclosene Sodium *(rINNM)*

Dicloroisocianurato sódico; Sodium Dichloroisocyanurate; Sodium Dichloro-*s*-triazinetrione; Sodium Troclosene; Troclosène Sodique; Trocloseno sódico; Troclosenum Natricum; Троклозен Натрий.
$C_3Cl_2N_3NaO_3$=219.9
CAS — 2893-78-9.
UNII — 07M9U9U0LK.

Profile

Troclosene sodium is a disinfectant with the general properties of chlorine (p. 1746.2) and sodium hypochlorite (p. 1768.3) but it remains active as pH increases from 6 to 10 and is reported to be less susceptible to inactivation by organic material. It contains about 56 to 65% of 'available chlorine' (see p. 1746.3).

Troclosene sodium is used for disinfecting hard surfaces (see Disinfection in Hepatitis and HIV Infection, p. 1731.2), babies' feeding bottles, and food and dairy equipment, for treating water (p. 1731.3), for rapid disinfection of swimming pools, for soft contact lens care (p. 1730.2), and in various commercial bleach detergents and scouring powders as a relatively stable source of chlorine.

Troclosene, troclosene potassium, and symclosene (trichloroisocyanuric acid $C_3Cl_3N_3O_3$ = 232.4) are similarly used.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Austral.*: Aquatabs; Milton; *Fr.*: Aquatabs; Steritabs; *Hong Kong*: Actichlor; *Israel*: K-sept; K-sorb; Klor-De; Oral-Blue†; Taharmayim; Taharsept; Tahartaf; *Ital.*: Dicloraster; *NZ*: Puritabs; *S.Afr.*: Softab†; *Singapore*: Biospot; *UK*: Milton; Presept.

Multi-ingredient Preparations. *Fr.*: Micropur Forte DCCNa.

Undebenzophene

Parahydroxybenzoate Phenoxyethanol; Undebenzofeno.
2-Phenoxyethyl *p*-hydroxybenzoate.
$C_{15}H_{14}O_4$=258.3
CAS — 55468-88-7.

Profile

Undebenzophene is an antiseptic that has been included in preparations intended for wound and burn disinfection.

Urea Hydrogen Peroxide

Carbamide Peroxide; Hydroperite; Peróxido de carbamida; Peróxido de hidrógeno y urea; Urea Peroxide; Гидроперит.
$NH_2CONH_2H_2O_2$=94.07
CAS — 124-43-6.
UNII — 31PZZVAU81.

Pharmacopoeias. In *US*.

USP 36: (Carbamide Peroxide). Store in airtight containers at a temperature not exceeding 40 degrees. Protect from light.

Profile

Urea hydrogen peroxide consists of hydrogen peroxide and urea in equimolecular proportions. It is used for the extemporaneous preparation of hydrogen peroxide. It is used for tooth whitening, and has been used for infections of the ear, mouth, skin, and mucous membranes and for softening ear wax.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Blanc Dient; Yadid; *Austral.*: Ear Clear; *Braz.*: Aceratum; *Ger.*: Elawox†; *Gr.*: Unisept; *Hong Kong*: Ear Clear; *Hung.*: Hyperol; *Irl.*: Exterol; *Israel*: Exterol; *Ital.*: Debrox; Dermoxyl; Ginoxil; *NZ*: Earclear; *Pol.*: Pertlenon; *UK*: Exterol; Otex; *USA*: Auraphene-B; Auro; Debrox; ERO; Gly-Oxide; Mollifene; Murine; Orajel Perioseptic.

Pharmacopoeial Preparations
USP 36: Carbamide Peroxide Topical Solution.

Zinc Peroxide

Peróxido de zinc; Zinc Dioxide; Zinc Superoxide; ZPO; Перекись Цинка; Цинк Пероксид.
ZnO_2=97.38
CAS — 1314-22-3.
UNII — 0I969DVM77.

Profile

The action of zinc peroxide is similar to that of hydrogen peroxide (p. 1755.2). Applied locally it has been used for disinfecting and deodorising burns, wounds, and various ulcers and lesions.

Preparations

Proprietary Preparations (details are given in Volume B)

Multi-ingredient Preparations. *Braz.*: Anaseptil; *Fr.*: Bioxyol; *Ital.*: Ektogan.

Electrolytes

Electrolytes are used to correct disturbances in fluid and electrolyte homoeostasis or acid–base balance and to re-establish osmotic equilibrium of specific ions. The osmotic effects of solutions may be expressed in terms of

- osmolality, which is defined as the 'molal' concentration in moles (or osmoles) per kg of solvent

or

- osmolarity, which is the 'molar' concentration in moles (or osmoles) per litre of solution

In clinical practice, solute concentrations are measured per litre of solution and are expressed as millimoles (mmol) per litre or sometimes as milliequivalents (mEq) per litre. Milliequivalents are converted to millimoles by dividing by the valency of the ion.

Positively charged ions are known as *cations* and include calcium, magnesium, potassium, and sodium ions. Negatively charged ions are known as *anions* and include bicarbonate, chloride, and phosphate ions. The ions principally involved in fluid and electrolyte homoeostasis and acid–base balance are sodium, chloride, bicarbonate, and potassium. Calcium, phosphate, and magnesium have a central role in the formation of bone mineral.

Acid–base Balance

Within the body, acid is mostly produced during cellular respiration in the form of carbon dioxide. Small amounts of various non-volatile acids are generated via metabolism, including lactic acid, uric acid, keto acids, and some inorganic acids such as sulfuric and phosphoric acids. For normal tissue function, the pH of the body needs to be held within a narrow range. The pH of arterial blood is normally maintained between about 7.38 and 7.42 by means of compensatory respiratory, renal, and buffering mechanisms.

The most important buffer system in the extracellular fluid is the bicarbonate-carbonic acid system. Bicarbonate and hydrogen ions are in equilibrium with carbonic acid which is in turn in equilibrium with carbon dioxide in the body fluid, as expressed by:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

A normal plasma-bicarbonate concentration in adults is in the range of 20 to 30 mmol/litre and arterial partial pressure of carbon dioxide (P_aCO_2) is normally 4.7 to 5.7 kPa (35 to 43 mmHg).

Ultimately, excess acid must be removed from the body and base regenerated. P_aCO_2 is under respiratory control with carbon dioxide being excreted by the lungs. Plasma-bicarbonate concentrations are regulated by the kidneys, where bicarbonate is actively regenerated or reabsorbed. Organic acids such as lactic acid may be eliminated by metabolism; and other non-volatile acids, such as the inorganic acids of phosphate and sulfate, are excreted via the kidneys with simultaneous regeneration of bicarbonate.

The relationship between plasma pH, P_aCO_2, and bicarbonate is defined by the Henderson-Hasselbalch equation which is used to assess acid–base balance.

For clinical purposes, this equation becomes

$$pH = pK_{CO2} + \log (C_{HCO3}/\alpha \times P_aCO_2)$$

where pH is the plasma pH, pK_{CO2} is the carbonic acid dissociation constant (6.1), C_{HCO3} is the plasma-bicarbonate concentration, α is a value representing carbon dioxide solubility, and P_aCO_2 is the arterial partial pressure of carbon dioxide. Disorders of acid–base balance may be due to a change in plasma-bicarbonate concentrations (metabolic) or to a change in P_aCO_2 (respiratory), although mixed disorders do occur.

The 4 major acid–base disturbances are:

- metabolic acidosis—a decrease in the plasma-bicarbonate concentration
- metabolic alkalosis—an increase in the plasma-bicarbonate concentration
- respiratory acidosis—hypoventilation and a raised P_aCO_2
- respiratory alkalosis—hyperventilation and a reduced P_aCO_2

A further measure that may provide useful information in the assessment of metabolic acidosis is the plasma anion gap. This is the difference in ionic charge between the principal plasma cation (sodium) and anions (chloride and bicarbonate), and provides an estimation of unmeasured serum anions, which include inorganic and organic acids.

References.

1. Gluck SL. Acid-base. *Lancet* 1998; 352: 474–9.
2. Hood VL, Tannen RL. Protection of acid-base balance by pH regulation of acid production. *N Engl J Med* 1998; 339: 819–26.
3. Kraut JA, Madias NE. Approach to patients with acid-base disorders. *Respir Care* 2001; 46: 392–403.
4. Epstein SK, Singh N. Respiratory acidosis. *Respir Care* 2001; 46: 366–83.
5. Foster GT, *et al.* Respiratory alkalosis. *Respir Care* 2001; 46: 384–91.
6. Madias NE, Adrogué HJ. Cross-talk between two organs: how the kidney responds to disruption of acid-base balance by the lung. *Nephron Physiol* 2003; 93: 61–6.
7. Wiseman AC, Linas S. Disorders of potassium and acid-base balance. *Am J Kidney Dis* 2005; 45: 941–9.

Metabolic acidosis. Metabolic acidosis, characterised by a low plasma-bicarbonate concentration and a tendency towards a fall in arterial pH, is the most frequent acid–base abnormality.

Metabolic acidosis with a *normal anion gap* is usually caused by excessive losses of bicarbonate from the gastrointestinal tract (as in severe diarrhoeas) or failure of the kidneys to reabsorb or regenerate adequate bicarbonate (as in the renal tubular acidoses). Ingestion of acidifying salts such as ammonium chloride, which generate hydrochloric acid, can also result in this type of acidosis. Metabolic acidosis characterised by an *increased anion gap* is often due to a reduction in the renal excretion of inorganic acids such as phosphates and sulfates as in renal failure (uraemic acidosis), or to the net accumulation of organic acids as, for example, in lactic acidosis or diabetic ketoacidosis.

Metabolic acidosis is diagnosed and monitored by measurement of serum electrolytes, arterial pH, and P_aCO_2. There is often hyperventilation with reduced cardiac function, constriction of peripheral veins, inhibition of the hepatic metabolism of lactate, and impairment of consciousness.

The main aim of **treatment** is to manage any underlying disorder,[1,2] and in some cases this will be sufficient to enable the body's homoeostatic mechanisms to correct the acid–base imbalance. The advantages of more active treatment of the acidosis must be balanced against the risks, including over-alkalinisation, and in consequence such therapy tends to be reserved for more persistent or severe cases.

The usual alkalinising agent is sodium bicarbonate. It may be given orally to replace bicarbonate losses in various chronic metabolic acidoses such as uraemic acidosis or renal tubular acidosis. Potassium bicarbonate may be preferred if the acidosis is associated with potassium deficiency. Potassium citrate and sodium citrate have also been used. More severe and acute cases (particularly where arterial pH is below 7.1) may require intravenous sodium bicarbonate therapy. Intravenous sodium bicarbonate has a role in acute metabolic acidoses attributable to severe renal failure, severe secretory diarrhoeas, and renal tubular acidosis. Although hypertonic solutions have been used, for example, in patients with circulatory overload, roughly isotonic bicarbonate solutions are otherwise preferred; arterial pH and plasma bicarbonate should be raised a little at a time and the patient's response monitored.

Although the role of bicarbonate is accepted in the forms of metabolic acidosis mentioned, its use in the treatment of metabolic acidosis with concomitant tissue hypoxia, particularly lactic acidosis, is controversial.[1-4] The administration of bicarbonate generates carbon dioxide which, if not appropriately eliminated, due to poor tissue perfusion or impaired ventilation or both, diffuses rapidly into the cells exacerbating intracellular acidosis. In addition, in metabolic addosis associated with organic acids such as lactic acid, there is a risk of over-alkalinisation due to the metabolism of the acid after correction of the arterial pH.

For similar reasons, the use of sodium bicarbonate in advanced cardiac life support (see Cardiac Arrest, p. 1268.3) is no longer routine, although current guidelines permit consideration of its use when cardiac arrest is associated with hyperkalaemia or tricyclic antidepressant overdose.

The role of bicarbonate in the management of diabetic ketoacidosis is also limited, although it may be appropriate in certain situations—see Diabetic Emergencies, p. 465.3.

Because of concerns about the effects of bicarbonate, other agents have been investigated for the treatment of metabolic acidosis, including trometamol (THAM) and sodium dichloroacetate.[1-4] Alkalinising agents that have to be metabolised to bicarbonate before they have an effect, such as sodium lactate, are not generally used as many patients with acute acidosis have impaired metabolic activity, particularly of lactate.

Peritoneal dialysis, haemodialysis, or haemofiltration is required for refractory metabolic acidosis associated with acute renal failure (p. 1779.1).

1. Swenson ER. Metabolic acidosis. *Respir Care* 2001; 46: 342–53.
2. Levraut J, Grimaud D. Treatment of metabolic acidosis. *Curr Opin Crit Care* 2003; 9: 260–5.
3. Arieff AI. Indications for use of bicarbonate in patients with metabolic acidosis. *Br J Anaesth* 1991; 67: 165–77.
4. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; 338: 26–34. Correction. *ibid.* 1999; 340: 247.

Metabolic alkalosis. Metabolic alkalosis with an increased plasma-bicarbonate concentration and a sustained elevation in arterial pH results from excessive renal reabsorption and/or regeneration of bicarbonate. It is commonly seen with volume contraction (chloride depletion), potassium depletion, or mineralocorticoid excess, and may occur with excessive alkali intake as in the milk-alkali syndrome. If the metabolic alkalosis is severe, cardiac arrhythmias and hypoventilation may develop and there can be symptoms of concomitant hypokalaemia such as muscle weakness.

Treatment is generally aimed at the underlying disturbances.[1-3] Correcting volume depletion by giving a chloride salt often obviates the need for other treatment; sodium chloride is normally used. However, potassium chloride may also be required if there is potassium depletion, particularly if this is severe. Rarely, direct acidification with ammonium chloride, dilute hydrochloric acid, or acidifying salts such as lysine hydrochloride or arginine hydrochloride may be required if the alkalosis is severe.

1. Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. *N Engl J Med* 1998; 338: 107–11.
2. Galla JH. Metabolic alkalosis. *J Am Soc Nephrol* 2000; 11: 369–75.
3. Khanna A, Kurtzman NA. Metabolic alkalosis. *Respir Care* 2001; 46: 354–65.

Calcium Homoeostasis

The adult body contains about 1.2 kg of calcium, of which about 99% is incorporated into the skeleton where its primary role is structural. The remaining 1% is found in body tissues and fluids and is essential for normal nerve conduction, muscle activity, and blood coagulation.

The concentration of calcium in plasma is normally kept within a narrow range (total calcium about 2.15 to 2.60 mmol/litre) by homoeostatic mechanisms involving parathyroid hormone, calcitonin, and vitamin D. Normally about 50% of calcium in plasma is in the ionised physiologically active form (giving a usual range of about 1.1 to 1.3 mmol/litre), about 10% is complexed with anions such as phosphate or citrate, and the remainder is bound to proteins, principally albumin. If the plasma-albumin concentration is raised (as in dehydration) or reduced (as is common in malignancy) it will affect the proportion of ionised calcium. Thus, the total plasma-calcium concentration is commonly adjusted for plasma albumin.

Hypercalcaemia. Hypercalcaemia, an increase in plasma-calcium concentration above the normal range, is most commonly due to primary hyperparathyroidism (p. 1170.3) or malignant disease.[1-4] Less common causes of hypercalcaemia include vitamin D intoxication, granulomatous diseases such as sarcoidosis, familial benign hypercalcaemia, renal failure, thyrotoxicosis, and excess calcium carbonate ingestion (milk-alkali or calcium-alkali syndrome).[1-4]

Mild asymptomatic hypercalcaemia is often associated with a plasma-concentration elevated above the normal but below 3.00 mmol/litre. Severe symptomatic hypercalcaemia is broadly correlated with a plasma-calcium concentration of more than 3.50 mmol/litre.

Symptoms of hypercalcaemia include thirst, polyuria, anorexia, constipation, muscle weakness, fatigue, and confusion. In severe cases, there may be nausea and vomiting; cardiac arrhythmias may develop but are rare. Extreme hypercalcaemia may result in coma and death. Chronic hypercalcaemia can lead to interstitial nephritis and calcium renal calculi.[3]

Mild asymptomatic hypercalcaemia is best corrected by increasing oral fluid intake and treating any identified underlying disease. Patients with more severe hypercalcaemia, and/or significant symptoms, need prompt **treatment** to reduce plasma-calcium concentrations independent of the cause.[2,3]

The first step is rehydration with intravenous sodium chloride 0.9% to restore the intravascular volume and to promote renal excretion of calcium. Loop diuretics will enhance calcium excretion, but are usually only given to prevent fluid overload or heart failure.[1-4] Thiazide diuretics should be avoided[2] as they increase the renal tubular reabsorption of calcium. Peritoneal dialysis or haemodialysis with calcium-free dialysate should be considered[2,4,5] in patients with renal failure for whom urinary excretion of calcium is inadequate.

In life-threatening hypercalcaemia, more specific immediate therapy is generally required in addition to saline.[2,3] Most experience has been gained in the treatment of hypercalcaemia of malignancy (p. 1167.2) using drugs that inhibit bone resorption, notably bisphosphonates.[1-5] Calcitonins have a rapid onset of action, but their effect is moderate and generally short-lived. Thus, they are seldom used alone, or as first-line agents; they may be given with bisphosphonates to rapidly lower serum calcium.[2,4] Plicamycin lowers serum calcium quickly but toxicity has limited its use.[2,3] Gallium nitrate is also effective when given continuously over several days; adverse effects such as nephrotoxicity are frequent and severe.[2,4] Corticosteroids are particularly effective for hypercalcaemia secondary to haematological malignancy, or associated with vitamin D toxicity, such as sarcoidosis.[1-5] They have been used to prolong the efficacy of calcitonin. Intravenous phosphates rapidly lower plasma-calcium concentrations but can cause soft tissue calcification (resulting in serious adverse effects such as irreversible renal damage and hypotension), and are best avoided.[2,3] Where intestinal calcium absorption is increased, dietary calcium and vitamin D intake should be restricted,[4,5] although some consider this unnecessary and ineffective.[1]

Choice of subsequent therapy is likely to depend on the specific cause.

1. Heath D. Hypercalcaemia. *Prescribers' J* 1999; 39: 234–41.
2. Bushinsky DA, Monk RD. Calcium. *Lancet* 1998; 352: 306–11.
3. Ralston SH, *et al.* Medical management of hypercalcemia. *Calcif Tissue Int* 2004; 74: 1–11.
4. Ariyan CE, Sosa JA. Assessment and management of patients with abnormal calcium. *Crit Care Med* 2004; 32 (suppl): S146–S154.
5. Inzucchi SB. Management of hypercalcemia: diagnostic workup, therapeutic options for hyperparathyroidism and other common causes. *Postgrad Med* 2004; 115: 27–36.

HYPERCALCAEMIA OF MALIGNANCY. About 10% of patients with cancer develop hypercalcaemia of malignancy, which is typically severe and progressive. Bisphosphonates are the preferred drugs for treating hypercalcaemia once the patient has been adequately rehydrated (see Hypercalcaemia of Malignancy, p. 1167.2).

HYPERPARATHYROIDISM. Excess secretion of parathyroid hormone in primary hyperparathyroidism (p. 1170.3) is characterised by hypercalcaemia, which is most frequently asymptomatic, and by hypophosphataemia. Oral phosphates and bisphosphonates have been used to control hypercalcaemia. However, in the long term, hypercalcaemia associated with primary hyperparathyroidism appears to be best managed by parathyroidectomy. Symptomatic hypocalcaemia may occur after surgery, requiring short-term treatment with calcium supplements and vitamin D.

VITAMIN D-MEDIATED HYPERCALCAEMIA. Hypercalcaemia can occur because of increased gastrointestinal absorption of calcium mediated by the active metabolite of vitamin D, 1,25-dihydroxycholecalciferol (calcitriol). This may be a feature of diseases associated with increased vitamin D sensitivity or increased vitamin D production, or may occur due to overdose of vitamin D. For example, granulomatous diseases such as sarcoidosis (p. 1612.2) are associated with unregulated production of 1,25-dihydroxycholecalciferol. Hypercalcaemia due to vitamin D is most commonly seen in patients with renal failure receiving vitamin D analogues such as ergocalciferol.

Treatment of severe hypercalcaemia requires prompt rehydration regardless of the cause (see Hypercalcaemia, above). Where hypercalcaemia is due to excessive doses of a vitamin D analogue, it should be discontinued until normocalcaemia is achieved. Corticosteroids effectively reduce gastrointestinal absorption of calcium, and these may be used intravenously as adjuncts to rehydration in severe hypercalcaemia, and orally for milder hypercalcaemia or longer term therapy. Oral sodium cellulose phosphate, which binds calcium in the gastrointestinal tract, and a low-calcium diet may also be considered. Oral chloroquine or hydroxychloroquine have been used in hypercalcaemia associated with sarcoidosis. Ketoconazole may be useful as an alternative to corticosteroids.

References.
1. Adams JS. Vitamin D metabolite-mediated hypercalcemia. *Endocrinol Metab Clin North Am* 1989; 18: 765–78.
2. Sharma OP. Vitamin D, calcium, and sarcoidosis. *Chest* 1996; 109: 535–9.

Hypocalcaemia. Hypocalcaemia, a decrease in plasma-calcium concentration below the normal range, may be due to impaired or reduced absorption of calcium from the gastrointestinal tract, as with vitamin D deficiency disorders (see Osteomalacia and Rickets, p. 1168.1) and chronic renal failure (see Renal Osteodystrophy, p. 1170.1). Alternatively, it may be due to deficient parathyroid hormone secretion and/or action as in hypoparathyroidism (p. 1171.2) and hypomagnesaemia (see below). Excessive phosphate administration is also a cause of hypocalcaemia (see Hyperphosphataemia, below). Rarely, hypocalcaemia may follow repeated infusions of citrate ions, for example, during transfusions utilising citrated blood, as the citrate complexes with the calcium ion. Respiratory alkalosis due to hyperventilation can also lead to depression of ionised plasma-calcium concentrations.

Where symptoms of hypocalcaemia occur, they are typically associated with increased neuromuscular excitability; paraesthesias can occur and in more severe cases, carpopedal spasm, muscle cramps, tetany, and convulsions may develop.[1-4] Other symptoms include ECG changes and mental disturbances such as irritability and depression. Prolonged hypocalcaemia can lead to dental defects, cataract formation, and in children can result in mental retardation.

In patients with hypocalcaemia due to an underlying disease, long-term management should be aimed at **treating** this disease. Vitamin D supplements are widely used to enhance calcium absorption and correct vitamin D deficiency disorders and hypoparathyroidism. Oral supplements of calcium salts are often also given. Acute hypocalcaemia or hypocalcaemic tetany require emergency treatment with intravenous calcium salts.[2-4]

1. Lebowitz MR, Moses AM. Hypocalcemia. *Semin Nephrol* 1992; 12: 146–58.
2. Reber PM, Heath H. Hypocalcemic emergencies. *Med Clin North Am* 1995; 79: 93–106.
3. Bushinsky DA, Monk RD. Calcium. *Lancet* 1998; 352: 306–11.
4. Cooper MS, Gittoes NJL. Diagnosis and management of hypocalcaemia. *BMJ* 2008; 336: 1298–1302. Correction. *ibid.*; available at http://www.bmj.com/cgi/content/full/336/7659/0-a (accessed 17/03/09) [dose]

Magnesium Homoeostasis

Magnesium is an essential body cation that is involved in numerous enzymatic reactions and physiological processes including energy transfer and storage, skeletal development, nerve conduction, and muscle contraction. Over half of the magnesium in the body is found in bone, about 40% is present in muscle and soft tissue, and only about 1% is present in the extracellular fluid. A normal concentration for magnesium in plasma is from about 0.7 to 1.0 mmol/litre.

Magnesium homoeostasis appears to be primarily regulated by the kidney where magnesium is extensively reabsorbed. Bone may act as a magnesium reservoir to reduce plasma-magnesium fluctuations. Magnesium is actively absorbed from the gastrointestinal tract and this is enhanced to some extent by 1,25-dihydroxycholecalciferol (calcitriol).

Hypermagnesaemia. Hypermagnesaemia is an increase in the plasma concentration of magnesium above the normal range, as may follow excessive parenteral doses of salts such as magnesium sulfate. Hypermagnesaemia due to oral intake is uncommon as the kidneys are able to excrete a relatively large magnesium load. However, it may occur in patients with impaired renal function taking large amounts of magnesium, for example, in antacids or laxatives.

Symptoms of hypermagnesaemia include nausea, vomiting, CNS and respiratory depression, hyporeflexia, muscle weakness, and cardiovascular effects including peripheral vasodilatation, hypotension, bradycardia, and cardiac arrest.

Treatment of mild hypermagnesaemia is usually limited to restricting magnesium intake. In severe hypermagnesaemia, ventilatory and circulatory support may be required. Slow intravenous injection of calcium gluconate is recommended to reverse the effects on cardiovascular and respiratory systems. If renal function is normal, adequate fluids should be given to promote renal magnesium clearance. This may be increased by the use of furosemide. Haemodialysis using a magnesium-free dialysis solution effectively removes magnesium, and this may be necessary in patients with renal impairment, or for whom other methods prove ineffective.

Hypomagnesaemia. Hypomagnesaemia, a plasma-magnesium concentration below the normal range, may result from a reduced magnesium intake as in dietary deficiency or malabsorption syndromes. Alternatively, it may be due to excessive magnesium loss, either via the kidney because of inadequate reabsorption, or more often from the gut, for example during chronic diarrhoea. Drugs that may cause renal magnesium wasting include aminoglycosides, amphotericin B, ciclosporin, cisplatin (see Effects on Electrolytes, p. 767.2), and diuretics.[1]

Hypomagnesaemia is closely associated with other electrolyte disturbances, especially hypocalcaemia (see above) and hypokalaemia (see p. 1777.2), and rarely occurs alone. Specific symptoms are therefore difficult to determine but may include anorexia, nausea, weakness, neuromuscular dysfunction such as tetany, tremor, and muscle fasciculations, and rarely seizures. Cardiac arrhythmias may occur, but the relative contribution of hypomagnesaemia and hypokalaemia to these is uncertain.

Magnesium salts can be given orally for the **treatment** of chronic or asymptomatic magnesium deficiency.[2,3] Parenteral therapy may be preferred in patients with poor gastrointestinal absorption of magnesium or who are unable to tolerate oral supplements (usually because they cause diarrhoea); magnesium sulfate can be given by intravenous or intramuscular injection. In acute symptomatic hypomagnesaemia, rapid replacement therapy with intravenous magnesium salts may be necessary. Renal function and plasma-magnesium concentrations should be monitored.

1. Atsmon J, Dolev E. Drug-induced hypomagnesaemia: scope and management. *Drug Safety* 2005; 28: 763–88.
2. Whang R, *et al.* Magnesium homeostasis and clinical disorders of magnesium deficiency. *Ann Pharmacother* 1994; 28: 220–6.
3. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; 352: 391–6.

Phosphate Homoeostasis

Phosphate is an essential bone mineral; about 80% of phosphorus in an adult body is incorporated into the skeleton as a calcium salt where it is required to give rigidity. The remainder is present in the soft tissues and is involved in several metabolic and enzymatic reactions including energy storage and transfer.

Phosphate exists in body fluids mainly as the divalent HPO_4^{2-} ion (about 80%) or monovalent $H_2PO_4^-$ ion (about 20%). Phosphate measurements are usually expressed as inorganic phosphorus to avoid confusion with the anion content. A normal range for phosphorus in plasma in adults is about 0.85 to 1.45 mmol/litre, but as only a small proportion of body phosphate is found in the extracellular fluid, plasma-phosphorus levels may not always reflect total body stores or predict replacement needs.

Phosphate concentrations in plasma are primarily regulated by renal excretion; parathyroid hormone reduces the renal tubular reabsorption of phosphate. Intestinal absorption of phosphate is enhanced by the vitamin D metabolite, 1,25-dihydroxycholecalciferol.

Hyperphosphataemia. Hyperphosphataemia, an abnormally raised plasma-phosphorus concentration, is usually associated with renal failure and may lead to renal osteodystrophy (p. 1170.1). Hyperphosphataemia may also be a consequence of release of phosphate from cells; this can occur in conditions of cell breakdown such as haemolysis or rhabdomyolysis, during chemotherapy (when it may be part of the tumour lysis syndrome), or as a result of acidoses. Hypoparathyroidism may also lead to hyperphosphataemia due to decreased levels of parathyroid hormone (see Hypoparathyroidism, p. 1171.2). Other causes include excessive phosphate doses during treatment of hypophosphataemia, overuse of phosphate enemas or oral phosphate bowel preparations, and excessive vitamin D intake.

Hyperphosphataemic symptoms include those of associated hypocalcaemia (see above). Complexation with calcium may lead to metastatic calcification.

The **treatment** of hyperphosphataemia[1,2] usually involves control of the relevant underlying condition, and the use of low-phosphate diets, and if necessary oral phosphate-binding agents, such as calcium acetate or carbonate or aluminium hydroxide. Sevelamer, a polymer

capable of binding phosphate, may also be given.[2,3] Lanthanum carbonate has also been used.[2-4] Haemodialysis has been used to correct hyperphosphataemia in renal failure.[4]

1. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; 352: 391–6.
2. Ritz E. The clinical management of hyperphosphatemia. *J Nephrol* 2005; 18: 221–8.
3. Bleyer AJ. Phosphate binder usage in kidney failure patients. *Expert Opin Pharmacother* 2003; 4: 941–7.
4. Albaaj F, Hutchison AJ. Hyperphosphataemia in renal failure: causes, consequences and current management. *Drugs* 2003; 63: 577–96.

Hypophosphataemia. Hypophosphataemia, a reduction in plasma-phosphorus concentrations below the normal range, may be due to insufficient absorption of phosphate or increased renal clearance as in primary hyperparathyroidism, vitamin D deficiency, or X-linked familial hypophosphataemia. An increased cell uptake of phosphate can also result in hypophosphataemia, for example in chronic respiratory alkalosis and related disorders including alcoholism, hepatic failure, and septicaemia. As phosphate is widely available in foods, dietary deficiency is rare though it may occur in infants of low birth-weight fed exclusively on human breast milk (see Rickets of Prematurity, p. 1792.1). The absorption of phosphate from the gastrointestinal tract can be reduced if phosphate-binding antacids are taken in large amounts.

Hypophosphataemia is usually asymptomatic but clinical symptoms become apparent when plasma-phosphorus concentrations fall below 0.3 mmol/litre.[1-4] Symptoms include neuromuscular dysfunction such as muscle weakness and paraesthesias, convulsions, cardiomyopathy, respiratory failure, and haematological abnormalities. Prolonged hypophosphataemia can result in rickets or osteomalacia (p. 1168.1).

Treatment of hypophosphataemia primarily involves correction of any underlying disease.[4] Milk or oral phosphate supplements may be appropriate if a phosphate deficiency is identified or in certain disorders such as X-linked hypophosphataemic rickets. Intravenous phosphate may be required for severe hypophosphataemia (see p. 1791.3), but this should be used cautiously to avoid hypocalcaemia and metastatic calcification.[2,3] Consideration should be given to correcting concomitant electrolyte disturbances such as hypomagnesaemia.

1. Larner AJ. Clinical applicability of inorganic phosphate measurements. *Br J Hosp Med* 1992; 48: 748–53.
2. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123–8.
3. Weisinger JR, Bellorín-Font E. Magnesium and phosphorus. *Lancet* 1998; 352: 391–6.
4. Gaasbeek A, Meinders AE. Hypophosphatemia: an update on its etiology and treatment. *Am J Med* 2005; 118: 1094–1101.

Potassium Homoeostasis

Potassium is mainly an intracellular cation, primarily found in muscle; only about 2% is present in the extracellular fluid. It is essential for numerous metabolic and physiological processes including nerve conduction, muscle contraction, and acid–base regulation. A normal concentration of potassium in plasma is about 3.5 to 5.0 mmol/litre, but factors influencing transfer between intracellular and extracellular fluids such as acid–base disturbances can distort the relationship between plasma concentrations and total body stores. The body content of potassium is primarily regulated by renal glomerular filtration and tubular secretion. Aldosterone enhances the renal secretion of potassium and other factors such as sodium excretion, dietary potassium intake, and plasma pH can modulate the excretion of potassium by the kidney. Insulin, $beta_2$ agonists, and aldosterone, and increases in plasma pH, can promote the cellular uptake of potassium. The passage of potassium into the cells and retention against the concentration gradient requires active transport via the Na^+/K^+ ATPase enzyme.

Hyperkalaemia. Hyperkalaemia, an abnormally raised plasma-potassium concentration, can occur if the potassium intake is increased, if the renal excretion decreases (as in renal failure or adrenocortical insufficiency), or if there is a sudden efflux of potassium from intracellular stores, (as in acidosis, or cell destruction due to tissue trauma, burns, haemolysis, or rhabdomyolysis). Renal failure is the commonest cause of severe hyperkalaemia.[1] Hyperkalaemia may also be induced by drugs such as the potassium-sparing diuretics, ciclosporin, tacrolimus, NSAIDs, or ACE inhibitors.[2,3] Usually the renal mechanisms for potassium excretion adapt readily to an increased potassium load, and hyperkalaemia due to increased dietary intake is rare unless renal function is also impaired.

Hyperkalaemia mainly affects the heart, but skeletal muscle function may also be affected. Symptoms include ECG abnormalities, ventricular arrhythmias, cardiac arrest, and also neuromuscular dysfunction such as muscle weakness and paralysis.[3,4]

Treatment involves giving calcium to counteract the negative effects of hyperkalaemia on cardiac excitability, drugs such as insulin or sodium bicarbonate to promote the transfer of potassium from the extracellular to the intracellar fluid compartment, and enhancing potassium excretion with exchange resins or dialysis.[3,4] The methods used depend largely on the severity of the hyperkalaemia and critically, any associated ECG changes. Hyperkalaemia associated with a plasma concentration of potassium above 6.0 to 7.0 mmol/litre or with ECG changes is usually considered a medical emergency.

If effects on the heart are present, then first-line therapy should be with a calcium salt given intravenously; typically, calcium gluconate is given by slow intravenous injection, the dosage being titrated and adjusted based on ECG improvement.

Calcium will not, however, reduce the plasma-potassium concentration. In moderate to severe hyperkalaemia, insulin, together with glucose to prevent hypoglycaemia, is given intravenously to reduce the potassium concentration by stimulating the uptake of potassium by cells.[1,5] Insulin is given as a rapid-acting soluble insulin and typical doses are 5 to 10 units with 50 mL of glucose 50% given slowly over 5 to 15 minutes. Doses may need to be repeated as necessary. Alternatively or additionally, intravenous sodium bicarbonate may be used to correct acidosis and promote cellular uptake of potassium (but see Metabolic Acidosis p. 1775.2). Opinions vary on its value[5] and on the appropriate dose and concentration, but it may be indicated where there is severe associated acidosis (pH less than 7.2).[1]

The $beta_2$ agonist, salbutamol, given intravenously or by a nebuliser, has also been found to enhance the cellular uptake of potassium and reduce plasma-potassium concentrations.[3-6] However, its effect may be inconsistent,[6] and some clinicians prefer to avoid $beta_2$ agonists because of fears that large doses may induce cardiac arrhythmias.[7] Some consider that it should only ever be used with insulin, as up to 40% of patients may not respond.[1]

After the plasma-potassium concentration has been reduced in the immediate term by enhancing cellular potassium uptake, treatments are often required that will remove excess potassium from the body over the longer term. Cation exchange resins such as calcium or sodium polystyrene sulfonate can be given orally or rectally and, after about 1 to 2 hours, will begin to remove potassium from the body, although the evidence to support their use is lacking.[5] Haemodialysis removes potassium from the body very effectively[5] and is particularly useful in patients with acute renal failure, hypervolaemia, hypernatraemia, or severe hyperkalaemia. Peritoneal dialysis is effective in some patients.

1. Ahee P, Crowe AV. The management of hyperkalaemia in the emergency department. *J Accid Emerg Med* 2000; 17: 188–91.
2. Perazella MA. Drug-induced hyperkalemia: old culprits and new offenders. *Am J Med* 2000; 109: 307–14.
3. Gennari FJ. Disorders of potassium homeostasis: hypokalemia and hyperkalemia. *Crit Care Clin* 2002; 18: 273–88.
4. Rastergar A, Soleimani M. Hypokalaemia and hyperkalaemia. *Postgrad Med J* 2001; 77: 759–64. Correction. *ibid.* 2002; 78: 126.
5. Mahoney BA, *et al.* Emergency interventions for hyperkalaemia. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 02/02/06).
6. Wong S-L, Maltz HC. Albuterol for the treatment of hyperkalemia. *Ann Pharmacother* 1999; 33: 103–6.
7. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; 352: 135–40.

HYPERKALAEMIC PERIODIC PARALYSIS. Hyperkalaemic periodic paralysis is an inherited disorder in which sudden increases in plasma-potassium concentrations cause muscle paralysis, sometimes followed by myotonia. An acute attack may require intravenous calcium gluconate and insulin with glucose (see Hyperkalaemia, above). Inhalation of a $beta_2$ agonist such as salbutamol has been used to treat or abort attacks.[1,2] Diuretics such as acetazolamide, diclofenamide, or the thiazides are used prophylactically to reduce the frequency of attacks.[2-4]

1. Hanna MG, *et al.* Salbutamol treatment in a patient with hyperkalaemic periodic paralysis due to a mutation in the skeletal muscle sodium channel gene (SCN4A). *J Neurol Neurosurg Psychiatry* 1998; 65: 248–50.
2. Bond EF. Channelopathies: potassium-related periodic paralyses and similar disorders. *AACN Clin Issues* 2000; 11: 261–70.
3. Meola G, Sansone V. Therapy in myotonic disorders and in muscle channelopathies. *Neurol Sci* 2000; 21 (suppl): S953–61.
4. Sansone V, *et al.* Treatment for periodic paralysis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/02/09).

Hypokalaemia. Chronic hypokalaemia, a prolonged reduction of the plasma concentration of potassium, usually indicates a reduction in total body potassium. It may result from an inadequate intake, or gastrointestinal losses, for example in patients with secretory diarrhoeas, or from excessive renal losses as in hyperaldosteronism, Cushing's syndrome, or chronic metabolic alkalosis. Thiazides or loop diuretics increase urinary-potassium losses. Other drugs, notably corticosteroids and some antibacterials such as gentamicin, also have this effect. Hypokalaemia can also be caused by an increased cellular uptake of potassium rather than excess body losses. This may occur with drugs such as $beta_2$ agonists or xanthines, during insulin therapy, acute alkalosis, or possibly be induced by catecholamines after myocardial infarction. Hypokalaemia secondary to hypomagnesaemia (see p. 1776.3) can occur.

Hypokalaemia results in neuromuscular disturbances ranging from muscle weakness to paralysis and respiratory insufficiency and can also cause rhabdomyolysis, ECG abnormalities, and ileus. Chronic hypokalaemia may lead to renal tubular damage (hypokalaemic nephropathy). Hypokalaemia increases the risk of digoxin toxicity.

Treatment involves correcting any underlying disorder and replacement therapy with potassium salts. Oral potassium supplements are generally preferred but in severe hypokalaemia associated with cardiac arrhythmias, paralysis or diabetic ketoacidosis, parenteral therapy may be necessary. Potassium salts, usually potassium chloride, may be given by intravenous infusion but must be administered slowly to avoid causing hyperkalaemia and associated cardiac toxicity; plasma-potassium concentrations should be closely monitored and ECG monitoring may be required. The choice of salt for oral potassium replacement depends on co-existing acid–base and electrolyte disturbances. Potassium chloride is generally the drug of choice for the treatment of hypokalaemia in patients with metabolic alkalosis with hypochloraemia, whereas a salt such as the bicarbonate may be preferred in patients with hyperchloraemic acidosis as in some renal tubular acidoses. Hypokalaemia secondary to hypomagnesaemia requires magnesium replacement therapy.

References.

1. Halperin ML, Kamel KS. Potassium. *Lancet* 1998; 352: 135–40.
2. Gennari FJ. Hypokalemia. *N Engl J Med* 1998; 339: 451–8.
3. Cohn JN, *et al.* New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med* 2000; 160: 2429–36.

BARTTER'S SYNDROME. Bartter's syndrome is a set of closely related disorders thought to result from inherited defects in ion transport in various sections of the renal tubule.[1,2] Patients exhibit hyperplasia of the juxtaglomerular cells, hypokalaemia and metabolic alkalosis, and excess aldosterone, prostaglandin, and renin production. Symptoms are primarily those of the hypokalaemia, including muscle weakness; polyuria and enuresis, and growth retardation in children, can occur. In contrast to other hyperreninaemic states, patients do not have hypertension or oedema.

Treatment rarely completely corrects hypokalaemia. Potassium supplementation may be given, while a cyclooxygenase inhibitor such as indometacin, or an ACE inhibitor such as captopril, can produce benefit.[2] Spironolactone and propranolol have also been tried and magnesium salts may be given if there is hypomagnesaemia.[2]

1. Guay-Woodford LM. Bartter syndrome: unraveling the pathophysiologic enigma. *Am J Med* 1998; 105: 151–61.
2. Amirlak I, Dawson KP. Bartter syndrome: an overview. *Q J Med* 2000; 93: 207–15.

DIURETIC-INDUCED HYPOKALAEMIA. Reduced potassium concentrations may result from the use of potassium-losing diuretics, particularly thiazides and loop diuretics. Clinically significant hypokalaemia is unlikely at the doses used in hypertension and the routine use of potassium supplements is no longer recommended. However, the concomitant use of a potassium-sparing diuretic such as amiloride or, less usually, a potassium supplement, may be necessary in patients at risk of hypokalaemia (see also Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.2).

HYPOKALAEMIC PERIODIC PARALYSIS. Hypokalaemic periodic paralysis is an inherited disorder in which episodes of hypokalaemia with muscle weakness or paralysis appear to be associated with a shift in potassium from the extracellular to the intracellular fluid. Acute attacks are treated with potassium, given orally or intravenously. Prophylaxis with acetazolamide[1,2] or diclofenamide[3] has been found to reduce the frequency and severity of attacks.

1. Ahlawat SK, Sachdev A. Hypokalaemic paralysis. *Postgrad Med J* 1999; 75: 193–7.
2. Bond EF. Channelopathies: potassium-related periodic paralyses and similar disorders. *AACN Clin Issues* 2000; 11: 261–70.
3. Sansone V, *et al.* Treatment for periodic paralysis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 19/02/09).

Sodium Homoeostasis

Sodium is the principal cation in the extracellular fluid and is responsible for the maintenance of the extracellular fluid volume and osmolality. In addition, sodium is also involved in nerve conduction, muscle contraction, acid–base balance, and cell nutrient uptake. A usual plasma concentration of sodium would be expected to be within 135 to 145 mmol/litre.

Sodium homoeostasis is complex and closely associated with fluid balance. The osmolality and volume of the extracellular fluid are tightly regulated. Small changes in osmolality (plasma-sodium concentrations) are corrected by alteration of extracellular volume. This balance of plasma osmolality is achieved by the secretion or suppression of antidiuretic hormone (ADH; vasopressin), which primarily controls water excretion by the kidney. A tendency towards

hyponatraemia suppresses ADH secretion and promotes renal loss of water; an increase in ADH secretion increases water reabsorption by the renal distal tubules. Changes in extracellular volume will also affect ADH release independently of osmolality. In addition, changes in extracellular volume result in modulation of the renal excretion of sodium.

Total body sodium content is regulated by renal sodium excretion, which can vary widely depending on dietary intake. Various mechanisms are involved in controlling renal sodium excretion including the renin-angiotensin system, glomerular filtration rate, and natriuretic factors. A reduction in extracellular fluid volume leads to the production of angiotensin II which stimulates the secretion of aldosterone. Aldosterone promotes the reabsorption of sodium ions by the distal tubules. There may be significant effects on sodium homoeostasis if adrenal insufficiency or mineralocorticoid excess disturb this mechanism.

Hypernatraemia. Hypernatraemia is an abnormal rise in the plasma-sodium concentration with a simultaneous rise in plasma osmolality. It is generally associated with volume depletion when water intake is less than water losses through renal or extrarenal routes. The causes include impaired thirst, as in coma or essential hypernatraemia, osmotic diuresis (solute diuresis), as in diabetic ketoacidosis (see Diabetic Emergencies, p. 465.3) or after drugs such as mannitol, and excessive water losses, either from the kidney, as in diabetes insipidus (p. 2348.2), or extrarenally, for example because of excessive sweating or diarrhoea.

Hypernatraemia can also occur after excessive oral sodium intake (but this is uncommon) and after inappropriate use of intravenous sodium chloride.

The clinical manifestations of hypernatraemia are caused by the effect of increased plasma osmolality on the brain and include somnolence, confusion, respiratory paralysis, and coma. CNS symptoms are more severe when hypernatraemia develops rapidly. If there is volume depletion, other symptoms such as hypotension, tachycardia, and symptoms of circulatory insufficiency may occur as well. A high volume of dilute urine is seen in patients with abnormal renal water conservation, whereas a low volume of concentrated urine is expected in patients with impaired thirst or excessive extrarenal water loss.

Treatment of hypernatraemia usually requires water replacement, and drinking water may be sufficient for some patients. In more severe conditions, glucose 5% may be given by slow intravenous infusion. Alternatively, some recommend the use of sodium chloride 0.9% if volume depletion is severe. Care is required, as too rapid correction can induce cerebral oedema, particularly in chronic conditions.

If the total body sodium is too high, loop diuretics may be used to increase sodium excretion, with fluid losses being replaced by an infusion of glucose 5% and potassium chloride. It has also been suggested that dialysis may be necessary if there is significant renal impairment, if the patient is moribund, or if the serum-sodium concentration is greater than 200 mmol/litre.

References.

1. Adrogué HJ, Madias NE. Hypernatremia. *N Engl J Med* 2000; 342: 1493–9.
2. Kang S-K, *et al.* Pathogenesis and treatment of hypernatremia. *Nephron* 2002; 92 (suppl): 14–17.
3. Reynolds RM, *et al.* Disorders of sodium balance. *BMJ* 2006; 332: 702–5.

Hyponatraemia. Hyponatraemia, an abnormal fall in the plasma-sodium concentration, usually with a simultaneous fall in the plasma osmolality, is not uncommon, and may occur in diseases as diverse as heart failure, cirrhosis, adrenocortical insufficiency, hyperglycaemia, and AIDS.

The kidney is able to conserve sodium, and sodium depletion due to low salt intake is rare. Sodium depletion may occur if there are abnormal losses, either from the gut as a consequence of repeated diarrhoea and/or vomiting or from the kidney, for example, due to various renal disorders or the overuse of diuretics (see under Hydrochlorothiazide, Effects on Electrolyte Balance, p. 1404.3).

The most common cause of hyponatraemia is dilution. This may result from excessive fluid intake, for example the ingestion of large volumes of water in patients with primary polydipsia (psychogenic polydipsia). More often, however, it is a result of reduced water excretion, as in renal impairment or the syndrome of inappropriate secretion of antidiuretic hormone (SIADH—p. 2351.2). Postoperative hyponatraemia is a frequent complication which can be exacerbated by the inappropriate intravenous use of hypotonic,[1] or even isotonic,[2] fluids.

Hyponatraemia due to sodium depletion in the presence of volume contraction may cause orthostatic hypotension and circulatory insufficiency. Dilutional hyponatraemia can be asymptomatic but headache, confusion, nausea, vomiting, somnolence, and weakness may occur. If severe, cerebral oedema may lead to respiratory arrest, convulsions, and coma. CNS symptoms are more common when the condition is acute.

Therapy is guided by the rate of development and degree of hyponatraemia, accompanying symptoms, and the state of water balance, and should also take into account the underlying cause. Mild asymptomatic hyponatraemia does not usually require specific therapy. Chronic mild to moderate sodium depletion, such as occurs in salt-losing bowel or renal disease, may be treated with oral sodium chloride supplements while ensuring adequate fluid intake.

When there is substantial volume depletion, volume replacement is necessary and intravenous sodium chloride 0.9% is often used.[3-5]

Chronic dilutional hyponatraemia, which is often asymptomatic, can generally be managed by correcting the underlying disease; water restriction may also be necessary and drugs that interfere with the action of ADH such as demeclocycline or lithium carbonate may be useful in SIADH.[3-6] Furosemide plus oral sodium chloride supplements have also been used.[7]

Acute symptomatic hyponatraemia (water intoxication) is generally associated with plasma-sodium concentrations below 120 mmol/litre and requires more aggressive therapy. This involves giving hypertonic or isotonic sodium chloride intravenously, often with a loop diuretic such as furosemide, especially if fluid overload is likely to be a problem.[4,6,7] The aim is to render the patient asymptomatic, with a plasma-sodium concentration of 120 to 130 mmol/litre; the plasma-sodium concentration should not be corrected to normal values nor should hypernatraemia be allowed to develop.[1,6,7] Plasma-sodium concentrations and the total body-water volume should be monitored throughout.

A rare neurological syndrome known as central pontine myelinolysis (osmotic demyelination) has been associated with the over-rapid correction of symptomatic hyponatraemia, particularly if the condition is well established. However, there is no consensus about the optimal administration of intravenous sodium chloride, and a number of regimens have been suggested. Generally, it has been recommended that the rate of correction of plasma-sodium should be 0.5 to 1 mmol/litre per hour, and not exceeding 2 mmol/litre per hour; maximum corrections have included 8 mmol/litre per 24 hours,[7] 12 mmol/litre per 24 hours or 18 mmol/litre over the first 48 hours,[6] and 20 mmol/litre in the first 48 hours.[1] Some[1,5] have given more specific recommendations depending on the severity of symptoms, suggesting that patients with severe symptoms, such as seizures, respiratory arrest, or neurogenic pulmonary oedema, require rapid correction in the first few hours, aiming for an initial increase in plasma-sodium of 2 to 4 mmol/litre, followed by a continuous infusion.

More recently, the vasopressin receptor antagonists conivaptan[5,6] and tolvaptan have become available for the management of euvolaemic and hypervolaemic hyponatraemia. Conivaptan is given intravenously whereas tolvaptan is given orally.

1. Moritz ML, Ayus JC. Hospital-acquired hyponatremia—why are hypotonic parenteral fluids still being used? *Nat Clin Pract Nephrol* 2007; 3: 374–82.
2. Steele A, *et al.* Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med* 1997; 126: 20–5.
3. Yeates KE, *et al.* Salt and water: a simple approach to hyponatremia. *CMAJ* 2004; 170: 365–9.
4. Reynolds RM, *et al.* Disorders of sodium balance. *BMJ* 2006; 332: 702–5.
5. Verbalis JG, *et al.* Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med* 2007; 120 (suppl 11A): S1–S21.
6. Cawley MJ. Hyponatremia: current treatment strategies and the role of vasopressin antagonists. *Ann Pharmacother* 2007; 41: 840–50.
7. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med* 2000; 342: 1581–9.

Dialysis Solutions

Soluciones para diálisis; Растворы Для Диализа.

Pharmacopoeias. In *Eur.* (see p. vii), which includes separate monographs for solutions for haemodialysis, haemofiltration and haemodiafiltration, and peritoneal dialysis.

Dialysis and Haemofiltration

Dialysis and filtration solutions are solutions of electrolytes formulated in concentrations similar to those of extracellular fluid or plasma. They always contain sodium and chloride and bicarbonate or a bicarbonate precursor. In addition, they often contain calcium and magnesium, and rarely potassium. Glucose may be added as an osmotic agent. These solutions allow the removal of water and metabolites and the replacement of electrolytes.

In *haemodialysis*, the exchange of ions between the solution and the patient's blood is made across a semipermeable membrane, primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by a pressure gradient. Membranes are either derived from cellulose (e.g. cuprophane) or are synthetic. Bicarbonate rather than a bicarbonate precursor is increasingly preferred as the bicarbonate source in haemodialysis since the problems of precipitation of calcium and magnesium have been overcome by changes in dialysis technique. Acetate is still used in some dialysers, but is thought to have vasodilator and cardiodepressant actions, and may not be converted to bicarbonate fast enough for high-flux haemodialysis or in patients with liver disease. Haemodialysis solutions are provided in a sterile concentrated form for dilution with water before use; this water need not be sterile.

In *peritoneal dialysis*, the exchange is made across the membranes of the peritoneal cavity primarily by diffusion. Excess fluid is removed by ultrafiltration achieved by the use of osmotic agents such as glucose. The problems of calcium bicarbonate precipitation have not yet been overcome, and lactate is generally used as the bicarbonate precursor. Peritoneal dialysis solutions must be sterile and apyrogenic.

In *haemofiltration*, blood is filtered rather than dialysed. Metabolites are removed by convective transport, and excess water by hydrostatic ultrafiltration. Fluid and electrolytes are replaced by direct intravenous infusion. Most haemofiltration solutions use acetate or lactate as the bicarbonate source. Haemofiltration solutions must be sterile and apyrogenic.

Uses and Administration

Dialysis and filtration procedures are used in renal failure to correct electrolyte imbalance, correct fluid overload, and remove metabolites. They also have a limited role in the treatment of overdosage and poisoning. The two main techniques are haemodialysis and peritoneal dialysis; haemofiltration is used less frequently. The choice of technique will depend on the condition to be treated, the clinical state of the patient, patient preference, and availability.

Haemodialysis is more efficient than peritoneal dialysis at clearing small molecules such as urea, whereas peritoneal dialysis may be better at clearing larger molecules. Haemodialysis is considered to be less physiological as it alternates periods of high clearance with periods of no clearance.

Haemodialysis is usually performed intermittently (often 3 times a week); a typical session takes 3 to 5 hours. More recently high-flux dialysers have been developed which have reduced the time required for dialysis sessions.

Peritoneal dialysis may be performed continuously or intermittently. Continuous ambulatory peritoneal dialysis (CAPD) is the most commonly used technique. Patients remain mobile, except during exchanges, and can carry out the procedure themselves. There is always dialysis solution in the peritoneal cavity, and this is drained and replaced 3 to 5 times daily. Continuous cycle peritoneal dialysis (CCPD) is similar, except that exchanges are carried out automatically overnight, and patients do not have to carry out any exchanges during the day. Intermittent peritoneal dialysis (IPD) requires the patient to be connected to a dialysis machine for 12 to 24 hours 2 to 4 times a week. During this time, dialysis solution is pumped into and out of the peritoneal cavity, with a dwell time of about 10 to 20 minutes.

Haemofiltration is usually performed as a continuous technique and, as it is not portable, its principal use is in intensive care units. It may also be used intermittently as an adjunct to haemodialysis in patients with excess fluid weight gain. Continuous arteriovenous or venovenous haemodiafiltration (CAVHD or CVVHD) combines dialysis and filtration.

Assessing serum concentrations of urea or creatinine before the next dialysis session is not a good measure of the adequacy of the dialysis, so various other measures have been developed including the urea reduction ratio and urea kinetic modelling. The use of such measures is more established for haemodialysis than for peritoneal dialysis.

References.

1. Zucchelli P, Santoro A. How to achieve optimal correction of acidosis in end-stage renal failure patients. *Blood Purif* 1995; 13: 375–84.
2. Carlsen DB, Wild ST. Grams to milliequivalents: a concise guide to adjusting hemodialysate composition. *Adv Ren Replace Ther* 1996; 3: 261–5.
3. Pastlick-Deetjen J, Kirchgessner J. Bicarbonate: the alternative buffer for peritoneal dialysis. *Perit Dial Int* 1996; 16 (suppl 1): S109–S113.
4. Pastan S, Bailey J. Dialysis therapy. *N Engl J Med* 1998; 338: 1428–37.
5. Ifudu O. Care of patients undergoing hemodialysis. *N Engl J Med* 1998; 339: 1054–62.
6. Mallick NP, Gokal R. Haemodialysis. *Lancet* 1999; 353: 737–42.
7. Gokal R, Mallick NP. Peritoneal dialysis. *Lancet* 1999; 353: 823–8.
8. Fischbach M, *et al.* Hemodialysis in children: principles and practice. *Semin Nephrol* 2001; 21: 470–9.
9. Schröder CH. The choice of dialysis solutions in pediatric chronic peritoneal dialysis: guidelines by an ad hoc European committee. *Perit Dial Int* 2001; 21: 568–74.
10. Teehan GS, *et al.* Update on dialytic management of acute renal failure. *J Intensive Care Med* 2003; 18: 130–8.
11. Locatelli F, *et al.* Optimal composition of the dialysate, with emphasis on its influence on blood pressure. *Nephrol Dial Transplant* 2004; 19: 785–96.

12. Lameire N. Volume control in peritoneal dialysis patients: role of new dialysis solutions. *Blood Purif* 2004; 22: 44–54.
13. Maduell F. Hemodiafiltration. *Hemodial Int* 2005; 9: 47–55.
14. Nanovic L. Electrolytes and fluid management in hemodialysis and peritoneal dialysis. *Nutr Clin Pract* 2005; 20: 192–201.
15. Saxena R. Peritoneal dialysis: a viable renal replacement therapy option. *Am J Med Sci* 2005; 330: 36–47. Correction. *ibid.*: 110.
16. Ikizler TA, Schulman G. Hemodialysis: techniques and prescription. *Am J Kidney Dis* 2005; 46: 976–81.

Acute renal failure. Acute renal failure (acute renal injury) is characterised by a rapid decline in kidney function, and has a variety of causes.[1-8] It is often classified by origin as *prerenal* (e.g. due to hypovolaemia such as that associated with shock, burns, or dehydration; congestive heart failure; or renal artery obstruction), *renal* (such as acute tubular necrosis or interstitial nephritis of various causes, including nephrotoxic drugs and infections), or *postrenal* (acute urinary tract obstruction). The prognosis depends on the underlying disease, which should be identified and treated if possible, but the mortality may still be as high as 60%, particularly after surgery or trauma and in patients who become oliguric. Management is essentially supportive in the hope that renal function will recover. Complications of acute renal failure include extracellular volume overload and hyponatraemia, hyperkalaemia, metabolic acidosis, hyperphosphataemia and hypocalcaemia. Those complications requiring urgent treatment, often including the use of dialysis, are severe hyperkalaemia (p. 1777.1), pulmonary oedema, pericarditis, and severe metabolic acidosis (p. 1775.2). The use of dialysis before clinical signs of uraemia is a matter of debate since it does not appear to hasten recovery *per se*,[1] but all save the shortest episodes of acute renal failure will require some form of renal replacement therapy with dialysis or filtration. Intermittent haemodialysis and peritoneal dialysis are both used, but the newer haemofiltration techniques have theoretical advantages in terms of volume control and cardiovascular stability, and are increasingly preferred.[2,9,10]

Numerous drugs have been tried in attempts to attenuate renal injury or hasten recovery in patients with acute tubular necrosis due to ischaemia or nephrotoxins.[1,5,11,12] These include drugs to increase renal blood flow (e.g. low-dose dopamine, atrial natriuretic peptide, or prostaglandins), drugs to increase urine flow and protect the epithelial cells (mannitol and loop diuretics, calcium-channel blockers), or the use of chelating agents or antidotes against specific nephrotoxins. Consistent clinical benefit has not, however, been shown and some would argue against the routine use of such drugs.[4]

Acute renal failure is reversible in about 95% of patients who survive the complications. A few patients who survive acute renal failure will require long-term dialysis or kidney transplantation (p. 1935.2).

1. Brady HR, Singer GG. Acute renal failure. *Lancet* 1995; 346: 1533–40.
2. Morgan AG. The management of acute renal failure. *Br J Hosp Med* 1996; 55: 167–70.
3. Evans JHC. Acute renal failure in children. *Br J Hosp Med* 1994; 52: 159–61.
4. Renal Association. Clinical practice guidelines Module 5: acute kidney injury 4th ed. (issued 2008). Available at: http://www.renal.org/pages/media/download_gallery/AKIguidelinesFINALjune08.pdf (accessed 17/03/09)
5. Dishart MK, Kellum JA. An evaluation of pharmacological strategies for the prevention and treatment of acute renal failure. *Drugs* 2000; 59: 79–91.
6. Ashley C, Holt S. Acute renal failure. *Pharm J* 2001; 266: 625–8.
7. Lameire N, *et al.* Acute renal failure. *Lancet* 2005; 365: 417–30.
8. Abuelo JG. Normotensive ischemic acute renal failure. *N Engl J Med* 2007; 357: 797–805.
9. McCarthy JT. Renal replacement therapy in acute renal failure. *Curr Opin Nephrol Hypertens* 1996; 5: 480–4.
10. Joy MS, *et al.* A primer on continuous renal replacement therapy for critically ill patients. *Ann Pharmacother* 1998; 32: 362–75.
11. Albright RC. Acute renal failure: a practical update. *Mayo Clin Proc* 2001; 76: 67–74.
12. Pruchnicki MC, Dasta JF. Acute renal failure in hospitalized patients: part II. *Ann Pharmacother* 2002; 36: 1430–42.

Chronic renal failure. Chronic renal failure is the irreversible, usually progressive, loss of renal function that eventually results in end-stage renal disease (ESRD) and the need for renal replacement therapy (dialysis or renal transplantation). The rate of decline in renal function is generally constant for each patient and is usually monitored by measuring serum-creatinine concentrations as an indirect index of the glomerular filtration rate (GFR). In its early stages when the patient is asymptomatic, progressive loss of renal function is described as diminished renal reserve or chronic renal insufficiency. When the limits of renal reserve have been exceeded and symptoms become apparent, it is termed chronic renal failure or overt renal failure. When renal function is diminished to such an extent that life is no longer sustainable (GFR less than 5 mL/minute), the condition is termed ESRD or uraemia. Many diseases can lead to ESRD, the most common being diabetic nephropathy (p. 465.1), glomerulonephritis (p. 1604.3), and hypertension (p. 1251.1).

The management of patients with chronic renal failure prior to ESRD involves measures to conserve renal function and compensate for renal insufficiency. Methods to slow the progression of renal failure include the treatment of hypertension (p. 1251.1), reduction of proteinuria, and the reduction of hyperlipidaemia (p. 1248.1). ACE inhibitors (p. 1284.1) or angiotensin II receptor antagonists (see Losartan, p. 1423.3) are used for the reduction of proteinuria and the control of hypertension. Dietary protein restriction (see Renal Failure, p. 2043.3) has also been used for control of proteinuria, but conclusive evidence for a renal protective effect is lacking. Anaemia (p. 1142.3), hyperphosphataemia (p. 1776.3), secondary hyperparathyroidism (p. 1170.3), and renal osteodystrophy (p. 1170.1) often require active treatment. Nephrotoxic drugs, including NSAIDs, should be avoided.

The choice between haemodialysis, peritoneal dialysis, and organ transplantation is considered, and the patient prepared, before it is actually required. In patients for whom transplantation is the preferred option, dialysis may still be required while waiting for a kidney. Kidney transplantation is discussed on p. 1935.2. There are differences between countries in the choice of dialysis technique for patients with ESRD. For example, in-centre haemodialysis is used in about 80% of patients in the USA, whereas CAPD is used in over 50% of patients in the UK. Overall survival appears to be similar between the 2 techniques, but more patients on CAPD will eventually require a change to another dialysis method because of treatment failure.

Unlike renal transplant patients, dialysis patients still require replacement therapy with hormones that are usually produced by the kidney. Thus, recombinant erythropoietin and hydroxylated vitamin D analogues are commonly given.

References.
1. NIH. Morbidity and mortality of dialysis. *NIH Consens Statement* 1993; 11: 1–33.
2. Friedman AL. Etiology, pathophysiology, diagnosis, and management of chronic renal failure in children. *Curr Opin Pediatr* 1996; 8: 148–51.
3. Steinman TI. Kidney protection: how to prevent or delay chronic renal failure. *Geriatrics* 1996; 51: 28–35.
4. Walker R. General management of end stage renal disease. *BMJ* 1997; 315: 1429–32.
5. McCarthy JT. A practical approach to the management of patients with chronic renal failure. *Mayo Clin Proc* 1999; 74: 269–73. Correction. *ibid.*: 538.
6. Morlidge C, Richards T. Managing chronic renal disease. *Pharm J* 2001; 266: 655–7.
7. Currie A, O'Brien P. Renal replacement therapies. *Pharm J* 2001; 266: 679–83.
8. Ruggenenti P, *et al.* Progression, remission, regression of chronic renal diseases. *Lancet* 2001; 357: 1601–8.
9. Taal MW. Slowing the progression of adult chronic kidney disease: therapeutic advances. *Drugs* 2004; 64: 2273–89.
10. Meguid El Nahas A, Bello AK. Chronic kidney disease: the global challenge. *Lancet* 2005; 365: 331–40.
11. Rabindranath KS, *et al.* Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2006 (accessed 20/02/09).
12. Renal Association. Clinical practice guidelines Module 1: chronic kidney disease. 2nd ed. (issued 2007). Available at: http://www.renal.org/Libraries/Guidelines/1_-_CKD_Current_version.sflb.ashx (accessed 20/08/10)

Electrolyte disturbances. Haemodialysis with magnesium-free dialysis solution has been used to remove magnesium from the body in severe hypermagnesaemia (p. 1776.2). Similarly, haemodialysis, and sometimes peritoneal dialysis, has been used in treating hypercalcaemia (p. 1776.1), hyperkalaemia (p. 1777.1), hypernatraemia (p. 1778.1), and hyperphosphataemia (p. 1776.3).

Overdosage and poisoning. Haemodialysis, or less often peritoneal dialysis, can be used to remove some substances from the body after overdosage or poisoning. Substances most readily removed have a low molecular weight, low volume of distribution, low protein binding, high water solubility, and high renal clearance. Examples of agents for which haemodialysis may have a role in the treatment of severe overdosage include alcohol (p. 1734.1), ethylene glycol (p. 2500.3), methyl alcohol (p. 2196.3), lithium (p. 430.2), and salicylates such as aspirin (p. 24.2). Dialysis may be particularly important when poisoning with these agents is complicated by renal failure.

Adverse Effects

Adverse effects occurring during *haemodialysis* include nausea, vomiting, hypotension, muscle cramps, and air embolus. Effects related to vascular access include infection, thrombosis, and haemorrhage. Adverse effects occurring during *haemofiltration* are similar to those for haemodialysis.

The most common adverse effects associated with *peritoneal dialysis* include peritonitis, hernias, hyperglycaemia, protein malnutrition, and catheter complications.

Long-term complications in dialysed patients, some of which may relate to renal failure itself, include haemodialysis-related amyloidosis, acquired cystic kidney disease, and accelerated atherosclerosis. Dialysis dementia is a special hazard of aluminium overload. Long-term peritoneal dialysis results in progressive structural changes to the peritoneal membrane ultimately resulting in dialysis failure.

References.
1. Himmelfarb J. Hemodialysis complications. *Am J Kidney Dis* 2005; 45: 1122–31.

Aluminium overload. Accumulation of aluminium in patients on dialysis may result in dialysis dementia, anaemia, and aluminium-related bone disease (see also p. 2439.2). Sources of aluminium include the water used for preparation of dialysis fluids and aluminium-containing phosphate binders used in treating renal osteodystrophy (p. 1170.1). It is therefore important that water used for the preparation of dialysis fluids has a low aluminium concentration; Ph. Eur. 8 specifies a limit for aluminium of 10 micrograms/litre. Non-aluminium-containing phosphate binders such as calcium acetate or calcium carbonate may be preferred for long-term therapy. Aluminium overload in patients on dialysis has been treated with desferrioxamine (p. 1544.3).

Copper toxicity. Liver and haematological toxicity has occurred as a result of absorption of copper from dialysis fluids (see Adverse Effects of Copper, p. 2058.1).

Haemodialysis-induced cramp. Muscle cramps (see Muscle Spasms, p. 2014.1) commonly occur during haemodialysis procedures and between sessions. Cramping usually affects the lower extremities, causing severe pain, and is a common reason for avoiding or stopping haemodialysis. The aetiology is not clear but possibly related to hypovolaemia, hypotension, changes in plasma osmolality, and hyponatraemia.[1]

Non-pharmacological measures to treat cramp during haemodialysis include the local application of moist heat and massage, and stretching the affected muscle. If present, hypotension should be corrected, by slowing or stopping ultrafiltration, and possibly giving isotonic or hypertonic sodium chloride infusion.[1] Midodrine has also been used for the management of hypotension.[2] Hypertonic solutions of sodium chloride or glucose may be used to raise plasma osmolality; mannitol has also been used but may accumulate in the extracellular space.[1]

Quinine has been widely used for the prevention of haemodialysis-induced cramp, but it can cause serious adverse effects and such use has been discouraged.[1] Other treatments that have been tried as prophylaxis include carnitine, creatine, and vitamins C and E. However, information on these is limited and data on long-term efficacy and safety are lacking.[1] There is also limited evidence that a traditional herbal medicine, shao-yao-gan-cao-tang (shakuyaku-kanzo-to), comprising extracts of peony and liquorice roots, may be of benefit for both prevention and treatment of haemodialysis-induced cramp.[1]

1. Kobrin SM, Berns JS. Quinine—a tonic too bitter for hemodialysis-associated muscle cramps? *Semin Dial* 2007; 20: 396–401.
2. Prakash S, *et al.* Midodrine appears to be safe and effective for dialysis-induced hypotension: a systematic review. *Nephrol Dial Transplant* 2004; 19: 2553–8.

Hypersensitivity. For anaphylactic reactions associated with the use of ethylene oxide for the disinfection of dialysis equipment, see p. 1751.3.

Infections. Patients undergoing haemodialysis are at risk of infections from microbial contamination of dialysis fluid, and from inadequate care of vascular access sites. Maximum microbial counts and limits for endotoxins have been specified for water used in dialysis fluids. Bicarbonate-based dialysis solutions are more susceptible to microbial growth than acetate-based solutions.

Peritonitis is common in patients receiving peritoneal dialysis. The risk of infection may be minimised by using disconnect systems, good aseptic technique, and by good care of catheters. Treatment of bacterial peritonitis requires intraperitoneal antibacterials, which are usually added to the dialysis fluid (see PD Peritonitis, under Peritonitis, p. 197.2).

Dialysis equipment should be regularly disinfected with agents such as formaldehyde (p. 1752.2) or ethylene oxide (p. 1751.2), but for mention of ethylene oxide anaphylactoid reactions, see p. 1751.3.

Metabolic complications. The high concentrations of glucose in peritoneal dialysis solutions required to form an osmotic gradient can lead to weight gain, hyperglycaemia, hyperlipidaemia, and increased protein loss. Alternative osmotic agents such as icodextrin (p. 2059.2) can be used, and amino acid-based solutions are also available.

References.
1. Burkart J. Metabolic consequences of peritoneal dialysis. *Semin Dial* 2004; 17: 498–504.

Precautions

Peritoneal dialysis is not appropriate for patients with abdominal sepsis, previous abdominal surgery, or severe inflammatory bowel disease.

Haemodialysis should be used with caution in patients with unstable cardiovascular disease or active bleeding. During haemodialysis and haemofiltration, heparin (see Extracorporeal Circulation, p. 1398.2) or epoprostenol (Uses, p. 1375.1) are required to prevent clotting of the blood in the extracorporeal circuit.

Dialysis solutions should be warmed to body temperature with dry heat because wet heat carries a risk of microbial contamination.

Interactions

The effects of dialysis and filtration procedures on drug concentrations in the body can be complex. More drug may be removed by one dialysis technique than another. In general, drugs of low molecular weight, high water solubility, low volume of distribution, low protein binding, and high renal clearance are most extensively removed by dialysis. For example, aminoglycosides are extensively removed by dialysis procedures, and extra doses may be needed to replace losses. Specific drug dosage adjustments for dialysis procedures may be used where these are known. For drugs where the effect of dialysis is unknown, it is usual to give maintenance doses after dialysis. Dialysis has been used to remove some drugs in the treatment of overdosage and poisoning (see p. 1779.2).

Dialysis-induced changes in fluids and electrolytes have the potential to alter the effects of some drugs. For example, hypokalaemia predisposes to digoxin toxicity.

In patients undergoing peritoneal dialysis, drugs such as insulin and antibacterials may be added to the dialysis fluid. Consideration should be given to the possibility of adsorption of drugs onto the PVC bags.

References.
1. Aronson JK. The principles of prescribing in renal failure. *Prescribers' J* 1992; 32: 220–31.
2. Cotterill S. Antimicrobial prescribing in patients on haemofiltration. *J Antimicrob Chemother* 1995; 36: 773–80.
3. Aronoff GR, *et al. Drug prescribing in renal failure: dosing guidelines for adults*. 4th ed. Philadelphia: American College of Physicians, 1999.

Preparations

Pharmacopoeial Preparations
Ph. Eur.: Solutions for Haemodialysis; Solutions for Haemofiltration and for Haemodiafiltration; Solutions for Peritoneal Dialysis.

Oral Rehydration Solutions

Soluciones de rehidratación oral; Растворы Для Пероральной Регидратации.

Oral rehydration solutions have 4 main constituents:
- electrolytes—typically sodium chloride and potassium chloride
- a bicarbonate source to correct or prevent metabolic acidosis, such as sodium bicarbonate or sodium citrate
- water to replace fluid losses
- a carbohydrate source to maximise absorption of fluid and electrolytes—typically glucose, although cereal-based formulations may also be used.

They are most commonly available as oral powders (oral rehydration salts) that are reconstituted with water before use, but effervescent tablets and ready-to-use oral solutions are also available.

Uses and Administration

Oral rehydration solutions are used for oral replacement of electrolytes and fluids in patients with dehydration, particularly that associated with acute diarrhoea of various aetiologies (p. 1805.2).

The dosage of oral rehydration solutions should be tailored to the individual based on body-weight and the stage and severity of the condition. The initial aim of treatment is to rehydrate the patient, and, subsequently, to maintain hydration by replacing any further losses due to continuing diarrhoea and vomiting and normal losses from respiration, sweating, and urination. Initial rehydration should be rapid, over 3 to 4 hours, unless the patient is hypernatraemic, in which case rehydration over 12 hours is appropriate.

For adults, a usual dose of 200 to 400 mL of oral rehydration solution for every loose motion has been suggested.

For dosage in children, see below.

Administration in children. Fluid and electrolytes may be replaced orally in children who are dehydrated, for example due to diarrhoea, using a dose of 200 mL of oral rehydration solution for every loose motion. In infants, the dose is 1 to 1.5 times their usual feed volume. Normal feeding can continue after the initial fluid deficit has been corrected. Breast feeding should continue between administrations of oral rehydration solution.

Sodium content and osmolarity. The original standard WHO oral rehydration solution contained 90 mmol/litre of sodium and 111 mmol/litre of glucose.[1-3] While it has been used safely and effectively,[4] it does not reduce the volume or duration of diarrhoea,[3] and solutions with reduced sodium content and osmolarity have been suggested to be more effective.[1,2] WHO and UNICEF now recommend a solution containing 75 mmol/litre of sodium and 75 mmol/litre of glucose, with a reduced osmolarity.[4] However, there have been concerns that the reduced sodium content of this formulation may increase the risk of hyponatraemia in patients with cholera,[3,5,6] and especially in adults.[4] WHO and UNICEF have stated that hyponatraemia may also occur with the standard WHO formulation, and that there is no evidence to suggest that this transient hyponatraemia has had significant adverse clinical consequences for cholera patients.[4] Solutions containing less sodium have been recommended in more developed countries: 60 mmol/litre in Europe,[7] and 45 to 90 mmol/litre in the USA.[8]

For discussion of modified formulations of oral rehydration solutions in the treatment of diarrhoea, including the use of cereal-based and low osmolarity preparations, see oral rehydration therapy under Diarrhoea, p. 1805.2.

1. Hahn S, *et al.* Reduced osmolarity oral rehydration solution for treating dehydration caused by acute diarrhoea in children. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 21/06/05).
2. CHOICE Study Group. Multicenter, randomized, double-blind clinical trial to evaluate the efficacy and safety of a reduced osmolarity oral rehydration salts solution in children with acute watery diarrhea. *Pediatrics* 2001; 107: 613–18.
3. Fuchs GJ. A better oral rehydration solution? An important step, but not a leap forward. *BMJ* 2001; 323: 59–60.
4. Anonymous. New oral rehydration solution adopted by WHO and UNICEF. *WHO Drug Inf* 2004; 18: 138–40.
5. Hirschhorn N, *et al.* Formulation of oral rehydration solution. *Lancet* 2002; 360: 340–1.
6. Cash R, *et al.* Oral rehydration and hyponatraemia. *Lancet* 1999; 354: 1733–4.
7. Booth I, *et al.* Recommendations for composition of oral rehydration solutions for the children of Europe: report of an ESPGAN working group. *J Pediatr Gastroenterol Nutr* 1992; 14: 113–15.
8. King CK, *et al.* Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. *MMWR* 2003; 52 (RR-16): 1–16. Also available at: http://www.cdc.gov/mmwr/PDF/rr/rr5216.pdf (accessed 20/08/10)

Oral versus intravenous rehydration. Although intravenous rehydration is advised for patients with the most severe dehydration (see Diarrhoea, p. 1805.2) it is also widely used in some countries in the management of less severe degrees of fluid loss.[1,2] However, a meta-analysis of 16 randomised controlled studies in children with gastroenteritis (5 of which included children with severe dehydration) found that oral or nasogastric rehydration with an appropriate rehydration solution was at least as effective as intravenous rehydration in terms of weight gain and intestinal losses, and was associated with a lower incidence of adverse effects and a reduced length of hospital stay.[3] The authors concluded that there was no evidence to support the ongoing use of intravenous rehydration in most cases of childhood gastroenteritis.

1. Elliott EJ, *et al.* Pre-admission management of acute gastroenteritis. *J Paediatr Child Health* 1996; 32: 18–21.
2. Pond-Jones EL, *et al.* Hospitalization for community-acquired, rotavirus-associated diarrhea: a prospective, longitudinal, population-based study during the seasonal outbreak. *Arch Pediatr Adolesc Med* 2000; 154: 578–85.
3. Fonseca BK, *et al.* Enteral vs intravenous rehydration therapy for children with gastroenteritis: a meta-analysis of randomized controlled trials. *Arch Pediatr Adolesc Med* 2004; 158: 483–90.

Adverse Effects

Vomiting can occur after taking oral rehydration solution, and may be an indication that it was given too quickly. If vomiting occurs, administration should be halted for 10 minutes then resumed in smaller, more frequent, amounts.

The risk of hypernatraemia or overhydration with oral rehydration solutions is low in patients with normal renal function. Overdosage of oral rehydration solutions in patients with renal impairment may lead to hypernatraemia and hyperkalaemia.

Precautions

Oral rehydration salts or effervescent tablets should be reconstituted only with water and at the volume stated. Fresh drinking water is generally appropriate, but freshly boiled and cooled water is preferred when the solution is for infants or when drinking water is not available. The solution should not be boiled after it is prepared. Other ingredients such as sugar should not be added. Unused solution should be stored in a refrigerator and discarded within 24 hours of preparation.

Oral rehydration solutions are not appropriate for patients with gastrointestinal obstruction, oliguric or anuric renal failure, or when parenteral rehydration therapy is indicated as in severe dehydration or intractable vomiting.

Preparations

Pharmacopoeial Preparations
BP 2014: Oral Rehydration Salts;
USP 36: Oral Rehydration Salts;
WHO/UNICEF: Oral Rehydration Salts.

Bicarbonate

Bicarbonato; Бикарбонат.

UNII — HN1ZRA3Q20.

Description. Bicarbonate is an alkalinising agent given as bicarbonate-containing salts (sodium or potassium bicarbonate) or bicarbonate-producing salts (acetate, citrate, or lactate salts). Allowance should be made for the effect of the cation.

Incompatibility. Bicarbonate-producing or bicarbonate-containing solutions have been reported to be incompatible with a wide range of drugs. In many cases this incompatibility is a function of the alkaline nature of the bicarbonate solution. Precipitation of insoluble carbonates may occur, as may production of gaseous carbon dioxide when the bicarbonate ion is reduced by acidic solutions.

Potassium Bicarbonate

Bicarbonato potásico; E501; Hidrogenocarbonato de potasio; Hydrogenuhličitan draselný; Kalii Hydrocarbonas; Kalii Hydrogenocarbobnas; Kalii hydrogenocarbonas; Kaliovandenillo karbonatas; Kálium-hidrogén-karbonát; Kaliumhydrogencarbonat; Kaliumvätekarbonat; Kaliumvetykarbonaatti; Monopotassium Carbonate; Potasio, bicarbonato de; Potassium, bicarbonate de; Potassium Hydrogen Carbonate; Potasu wodorowęglan; Potasyum Bikarbonat; Калий Бикарбонат; Бикарбонат Калия; Гидрокарбонат Калия; Двууглекислый Калий.

$KHCO_3$=100.1

CAS — 298-14-6.

ATC — A12BA04.

ATC Vet — QA12BA04.

UNII — HM5Z15LEBN.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Potassium Hydrogen Carbonate; Potassium Bicarbonate BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. When heated in the dry state or in solution, it is gradually converted to potassium carbonate. A freshly prepared 5% solution in water has a pH of not more than 8.6.

USP 36: (Potassium Bicarbonate). Colourless, odourless, transparent monoclinic prisms or white granular powder. Freely soluble in water; practically insoluble in alcohol. Its solutions are neutral or alkaline to phenolphthalein.

Equivalence. Each g of potassium bicarbonate represents about 10 mmol of potassium and of bicarbonate. Potassium bicarbonate 2.56 g is equivalent to about 1 g of potassium.

Potassium Citrate

Citrato tripotásico; Citronan draselný monohydrát; E332; Kalii citras; Kalii Citras Monohydricus; Kalio citratas; Kaliumcitrat; Kaliumsitraatti; Potasio, citrato de; Potassium, citrate de; Potasu cytrynian; Potasyum Sitrat; Trikálium-citrát; Tripotassium Citrate; Калий Цитрат; Лимоннокислый Калий.

Tripotassium 2-hydroxypropane-1,2,3-tricarboxylate monohydrate.

$C_6H_5K_3O_7,H_2O$=324.4

CAS — 866-84-2 (anhydrous potassium citrate); 6100-05-6 (potassium citrate monohydrate).

ATC — A12BA02.

ATC Vet — QA12BA02.

UNII — EE90ONI6FF (potassium citrate monohydrate); 86R1NVR0HW (anhydrous potassium citrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int.*, and *US.*

Ph. Eur. 8: (Potassium Citrate). Transparent, hygroscopic crystals or a white or almost white granular powder. Very soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Potassium Citrate). Transparent crystals or a white granular powder. It is odourless and is deliquescent in moist air. Soluble 1 in 1 of water and 1 in 2.5 of glycerol; almost insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of potassium citrate (anhydrous) represents about 9.8 mmol of potassium and 3.26 mmol of citrate. Each g of potassium citrate (monohydrate) represents about 9.3 mmol of potassium and 3.08 mmol of citrate. Potassium citrate (monohydrate) 2.77 g is equivalent to about 1 g of potassium.

Sodium Acetate

Acetato sódico; E262; Natrii Acetas; Natrii acetas trihydricus; Natrio acetatas trihidratas; Natrium Aceticum; Nátrium-acetát; Natriumacetat trihydrat; Natriumasetaattitrihydraatti; Octan sodný trihydrát; Sodio, acetato de; Sodium (acétate de) trihydraté; Sodu octan; Ацетат Натрия; Уксуснокислый Натрий.

$CH_3CO_2Na.3H_2O$=136.1

CAS — 127-09-3 (anhydrous sodium acetate); 6131-90-4 (sodium acetate trihydrate).

ATC — B05XA08.

ATC Vet — QB05XA08.

UNII — NVG71ZZ7P0 (anhydrous sodium acetate); 4550K0SC9B (sodium acetate trihydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*.

US also allows the anhydrous form.

Ph. Eur. 8: (Sodium Acetate Trihydrate). Colourless crystals. Very soluble in water; soluble in alcohol. A 5% solution in water has a pH of 7.5 to 9.0. Store in airtight containers.

USP 36: (Sodium Acetate). It contains three molecules of water of hydration or is anhydrous. Colourless, transparent crystals, or a white, granular crystalline powder, or white flakes. It is odourless or has a faint acetous odour. It is efflorescent in warm dry air. Soluble 1 in 0.8 of water, 1 in 0.6 of boiling water, and 1 in 19 of alcohol. pH of a solution in water containing the equivalent of 3% of anhydrous sodium acetate is between 7.5 and 9.2. Store in airtight containers.

Equivalence. Each g of sodium acetate (anhydrous) represents about 12.2 mmol of sodium and of acetate. Each g of sodium acetate (trihydrate) represents about 7.3 mmol of sodium and of acetate. Sodium acetate (anhydrous) 3.57 g is equivalent to about 1 g of sodium. Sodium acetate (trihydrate) 5.92 g is equivalent to about 1 g of sodium.

Sodium Acid Citrate

Disodium Hydrogen Citrate; Disodu wodorocytrynian; E331; Hidrogenocitrato de disodio; Natrium Citricum Acidum; Sodio, citrato ácido de; Цитрат Натрия Двузамещенный.

$C_6H_6Na_2O_7.1½H_2O$=263.1

CAS — 144-33-2.

UNII — 6FO62KCQ7A.

Pharmacopoeias. In *Br.*

BP 2014: (Sodium Acid Citrate). A white, odourless or almost odourless, powder. Freely soluble in water; practically insoluble in alcohol. A 3% solution in water has a pH of 4.9 to 5.2.

The BP gives Disodium Hydrogen Citrate as an approved synonym.

Equivalence. Each g of sodium acid citrate (sesquihydrate) represents about 7.6 mmol of sodium and 3.8 mmol of citrate. Sodium acid citrate (sesquihydrate) 5.72 g is equivalent to about 1 g of sodium.

Sodium Bicarbonate

Sodio, hidrogenocarbonato de; Baking Soda; Bicarbonato sódico; E500; Hidrogenocarbonato de sodio; Hydrogenuhličitan sodný; Monosodium Carbonate; Natrii Bicarbonas; Natrii Hydrogenocarbonas; Natrio vandenilio karbonatas; Nátrium-hidrogén-karbonát; Natriumhydrogencarbonat; Natriumvätekarbonat; Natriumvetykarbonaatti; Sal de Vichy; Sodium Acid Carbonate; Sodium bicarbonate de; Sodium Hydrogen Carbonate; Sodu wodoroweglan; Sodyum Bikarbonat; Питьевая Сода; бикарбонат Натрия; Гидрокарбонат Натрия; Двууглекислый Натрий.

$NaHCO_3$=84.01

CAS — 144-55-8.

ATC — B05CB04; B05XA02.

ATC Vet — QB05CB04; QB05XA02; QG04BQ01.

UNII — 8MDF5V39QO.

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 8: (Sodium Hydrogen Carbonate; Sodium Bicarbonate BP 2014). A white or almost white, crystalline powder. Soluble in water; practically insoluble in alcohol. The pH of a freshly prepared 5% solution in water is not more than 8.6. When heated in the dry state or in solution, it gradually changes into sodium carbonate.

USP 36: (Sodium Bicarbonate). A white crystalline powder that slowly decomposes in moist air. Soluble 1 in 12 of water; insoluble in alcohol. Its solutions, when freshly prepared with cold water, without shaking, are alkaline to litmus; alkalinity increases on standing, agitation, or heating.

Equivalence. Each g of sodium bicarbonate (anhydrous) represents about 11.9 mmol of sodium and of bicarbonate. Sodium bicarbonate 3.65 g is equivalent to about 1 g of sodium.

Sodium Citrate

Citrato trisódico; Citronan sodný dihydrát; E331; Natrii Citras; Natrii Citras Dihydricus; Natrio citratas; Natriumcitrat; Natriumsitraatti; Sodio, citrato de; Sodium, citrate de; Sodu cytrynian; Sodyum Sitrat; Trinátrium-citrát; Trisodium Citrate; Цитрат Натрия Трёхзамещенный.

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dihydrate.

$C_6H_5Na_3O_7.2H_2O$=294.1

CAS — 68-04-2 (anhydrous sodium citrate); 6132-04-3 (sodium citrate dihydrate).

ATC — B05CB02.

ATC Vet — QB05CB02.

UNII — RS7A450LGA (anhydrous sodium citrate); 1Q73Q2JULR (sodium citrate); B22547B95K (sodium citrate dihydrate).

Pharmacopoeias. In *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.*

Int. and *US* specify anhydrous or dihydrate.

Ph. Eur. 8: (Sodium Citrate). A white or almost white, crystalline powder or white or almost white, granular crystals; slightly deliquescent in moist air. Freely soluble in water; practically insoluble in alcohol. Store in airtight containers.

USP 36: (Sodium Citrate). It is anhydrous or contains two molecules of water of hydration. Colourless crystals, or a white crystalline powder. The hydrous form is soluble 1 in 1.5 of water and 1 in 0.6 of boiling water; insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of sodium citrate (anhydrous) represents about 11.6 mmol of sodium and 3.9 mmol of citrate. Each g of sodium citrate (dihydrate) represents about 10.2 mmol of sodium and 3.4 mmol of citrate. Sodium citrate (anhydrous) 3.74 g is equivalent to about 1 g of sodium. Sodium citrate (dihydrate) 4.26 g is equivalent to about 1 g of sodium.

Storage. Sterilised solutions when stored may cause separation of particles from glass containers and solutions containing such particles must not be used.

Sodium Lactate

E325; Lactato de sodio; Lactato sódico; Natrii Lactatis; Natriumlaktaatti; Natriumlaktat; Sodium, lactate de; Лактат Натрия; Молочнокислый Натрий.

Sodium 2-hydroxypropionate.

$C_3H_5NaO_3$=112.1

CAS — 72-17-3.

UNII — TU7HW0W0QT (sodium lactate); P2Y1C6M9PS (L-sodium lactate); FM1Z1J8373 (D-sodium lactate).

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), and *US* include preparations of sodium lactate.

Ph. Eur. 8: (Sodium Lactate Solution). It contains a minimum declared content of 50% w/w of sodium lactate and is a mixture of the two enantiomers in about equal proportions. Sodium (*S*)-Lactate Solution contains a minimum of 50% w/w of sodium lactate, not less than 95% of which is the (*S*)-enantiomer. The solutions are clear, colourless, slightly syrupy liquids. Miscible with water and with alcohol. pH 6.5 to 9.0.

USP 36: (Sodium Lactate Solution). It is an aqueous solution containing at least 50% sodium lactate. A clear, colourless or practically colourless, slightly viscous liquid, odourless or having a slight, not unpleasant, odour. Miscible with water. pH between 5.0 and 9.0. Store in airtight containers.

Equivalence. Each g of sodium lactate (anhydrous) represents about 8.9 mmol of sodium and of lactate. Sodium lactate (anhydrous) 4.88 g is equivalent to about 1 g of sodium.

Uses and Administration

Bicarbonate-providing salts are alkalinising agents used for a variety of purposes including the correction of metabolic acidosis, alkalinisation of the urine, and as antacids.

When an alkalinising agent is indicated for treating acute or chronic **metabolic acidosis** (p. 1775.2), sodium bicarbonate is usually used. In conditions when acute metabolic acidosis is associated with tissue hypoxia, such as *cardiac arrest* and *lactic acidosis*, the role of such alkalinising agents is controversial (see p. 1775.2, and for guidelines on advanced cardiac life support, see Cardiac Arrest, p. 1268.3). Sodium lactate has been given as an alternative to sodium bicarbonate in acute metabolic acidosis, but is no longer recommended because of the risk of precipitating lactic acidosis. In *chronic hyperchloraemic acidosis* associated with potassium deficiency, potassium bicarbonate may be preferred to sodium bicarbonate. The citrate salts of potassium or sodium have also been used as alternatives to sodium bicarbonate in treating chronic metabolic acidosis resulting from *renal disorders*. Sodium bicarbonate, lactate and acetate, and potassium acetate are used as bicarbonate sources in *dialysis fluids* (p. 1778.2).

The dose of bicarbonate required for the treatment of acidotic states must be calculated on an individual basis, and is dependent on the acid–base balance and electrolyte status of the patient. In the treatment of chronic acidosis, bicarbonate has been given orally and doses providing 57 mmol (4.8 g sodium bicarbonate) or more daily may be required. In severe acidosis, sodium bicarbonate has been given intravenously by continuous infusion usually as a 1.26% (150 mmol/litre) solution or by slow intravenous injection of a stronger (hypertonic) solution of up to 8.4% (1000 mmol/litre) sodium bicarbonate (but see the discussion on metabolic acidosis, p. 1775.2). For the correction of acidosis during advanced cardiac life support procedures, doses of 50 mmol of sodium bicarbonate (50 mL of an 8.4% solution) may be given intravenously to adults. Frequent monitoring of serum-electrolyte concentrations and acid–base status is essential during treatment of acidosis.

Sodium bicarbonate may be used in the management of **hyperkalaemia** (p. 1777.1) to promote the intracellular uptake of potassium and correct associated acidosis, although there is some debate as to its value. Some sources suggest that 50 to 100 mL of an 8.4% solution may be given in severe hyperkalaemia accompanied by acidosis, although more dilute solutions have been used, and care is required, particularly if there is accompanying renal impairment.

Sodium bicarbonate, sodium citrate, and potassium citrate cause **alkalinisation of the urine.** They may therefore be given to relieve discomfort in mild *urinary-tract infections* (p. 213.1) and to prevent the development of uric-acid renal calculi in the initial stages of *uricosuric* therapy for hyperuricaemia in chronic gout (for example, see Precautions for Probenecid, p. 608.1). In both cases, they are given with a liberal fluid intake, usually orally, in divided doses of up to about 10 g daily. Sodium bicarbonate may also be used to alkalinise the urine in *acute poisoning* with weakly acidic drugs such as salicylates and phenoxyacetate pesticides; use with a diuretic for 'forced alkaline diuresis' is no longer recommended.

When given orally, sodium bicarbonate and potassium bicarbonate neutralise acid secretions in the gastrointestinal tract and sodium bicarbonate in particular is therefore frequently included in **antacid** preparations (p. 1803.1). To relieve *dyspepsia* doses of about 1 to 5 g of sodium bicarbonate in water have been taken when required. Sodium citrate has been widely used as a 'clear' (non-particulate) antacid, usually with an H_2-antagonist, for the *prophylaxis of acid aspiration* associated with anaesthesia (p. 1804.2). Sodium bicarbonate is also used in various preparations for *double-contrast radiography* where production of gas (carbon dioxide) in the gastrointestinal tract is necessary. Similarly, solutions containing sodium bicarbonate or citrate have been used to treat acute *oesophageal impaction*.

Sodium bicarbonate and sodium or potassium citrate are used as buffering or alkalinising agents in *pharmaceutical formulation*. Sodium or potassium bicarbonate and anhydrous sodium citrate are used in effervescent tablet formulations.

Individual salts also have **other specific uses.** A 5% solution of sodium bicarbonate can be administered as ear drops to soften and remove *ear wax* (see under Docusates, p. 1836.3). Sodium bicarbonate injection has been used to treat *extravasation of anthracycline antineoplastics* (p. 731.3) although as mentioned in Adverse Effects, p. 1782.2, hypertonic solutions may themselves cause necrosis.

Sodium citrate has anti-clotting properties and is used, as sodium acid citrate, with other agents in solutions for the anticoagulation and preservation of blood for *transfusion* purposes. Similarly, sodium citrate 3% irrigation may be useful for the dissolution of *blood clots in the bladder* as an alternative to sodium chloride 0.9%. Enemas containing sodium citrate are given rectally as *osmotic laxatives*. Sodium citrate is also a common ingredient in *cough* mixtures. Eye drops containing sodium citrate 10% have been used in the treatment of chemical *eye burns* (p. 1782.1); they may be used with potassium ascorbate eye drops (see Uses of Vitamin C Substances, p. 2111.1).

Eye disorders. Sodium bicarbonate is used in the management of blepharitis, an inflammation of the margin of the eyelids with various causes. It may be allergic in nature or associated with seborrhoea of the scalp. Infection of the eyelids can produce ulcerative blepharitis, a condition characterised by the formation of yellow crusts which may glue the eyelashes together. Parasites occasionally cause blepharitis. The condition is first treated by cleaning the eyes and eyelids with sodium bicarbonate solution or a suitable bland eye lotion; simple eye ointment or diluted baby shampoo can also be used to soften crusts to aid removal. If an infection is present, antibacterials may be required (p. 182.1). Long-term management consists of daily cleansing of the lid margins with a bland eye lotion.

EYE BURNS. Both heat and chemicals can burn the eye, causing damage to the conjunctiva, cornea, and underlying structures. Burn severity may be influenced by the amount of burning substance that enters the eye and the duration of contact, its temperature and impact force, whether it is a liquid or solid, its pH, and osmolarity.[1,2] Hydrofluoric acid, sulfurous acid, and alkalis readily penetrate the corneal stroma.[2] Immediate irrigation is essential, and a duration of at least 15 to 30 minutes is recommended; it may need to be repeated periodically. Water or sodium chloride 0.9% solution may be used initially, but because they are hypotonic to the eye there can be an increased uptake of the fluid and diffusion of the burning substance into the deeper layers of the cornea, resulting in oedema. To reduce this risk solutions with higher osmolarities have been suggested, if available, and include balanced salt solution, buffered solutions such as lactated Ringer's solution, and commercial decontamination preparations with amphoteric and chelating properties.[1,2]

For acid and alkali burns ascorbate and citrate eye drops have been tried, and ascorbate given orally, based on suggestions that ascorbate may scavenge free radicals and citrate may reduce the release of free radicals and proteolytic enzymes in burn tissue.[1] However, a retrospective analysis of 121 patients with alkali burns to the eye suggested those with less severe burns (grades 1 and 2) did not benefit from an intensive topical therapy regimen including 10% ascorbate drops and 10% citrate drops;[3] a trend to more rapid healing and better visual outcome were seen in patients with grade 3 burns but in those with the most severe damage (grade 4) the regimen made no difference. In the management of hydrofluoric acid burns of the eye, Hexafluorine has been used for irrigation (but see p. 2529.2). Other general treatments that may be required include topical application of anaesthesia, corticosteroids, and antibacterials, treatment for glaucoma, and surgery.[1,2]

1. Schrage NF, *et al.* Eye burns: an emergency and continuing problem. *Burns* 2000; 26: 689–99.
2. Ruckenkorn R, *et al.* Emergency treatment of chemical and thermal eye burns. *Acta Ophthalmol Scand* 2002; 80: 4–10.
3. Brodovsky SC, *et al.* Management of alkali burns: an 11-year retrospective review. *Ophthalmology* 2000; 107: 1829–35.

Osteoporosis. Potassium bicarbonate in an oral dose of 1 to 2 mmol/kg daily improved mineral balance and bone metabolism in a short-term study.[1] However, the authors cautioned against the use of bicarbonate to treat or prevent osteoporosis (p. 1168.1) without further study.[2]

1. Sebastian A, *et al.* Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; 330: 1776–81.
2. Sebastian A, Morris RC. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. *N Engl J Med* 1994; 331: 279.

Renal calculi. Citrate forms soluble complexes with calcium, thereby reducing urinary saturation of stone-forming calcium salts. Potassium citrate has a hypocalciuric effect when given orally, probably due to enhanced renal calcium absorption. Urinary calcium excretion is unaffected by sodium citrate, since the alkali-mediated hypocalciuric effect is offset by a sodium-linked calciuresis.[1] Potassium citrate may be beneficial in reducing the rate of stone formation in patients with hypocitraturia[2,3] or hypercalciuria.[4] As mentioned in Uses on p. 1781.2, sodium bicarbonate or sodium or potassium citrate may also be used for their alkalinising action, as an adjunct to a liberal fluid intake, to prevent development of uric-acid renal calculi during uricosuric therapy.

Other causes of renal calculi and their treatment are discussed on p. 2350.3.

Urinary alkalinisation with potassium bicarbonate or potassium citrate may be useful in the management of cystine stone formation in patients with cystinuria (see under Penicillamine, p. 1567.2).

1. Anonymous. Citrate for calcium nephrolithiasis. *Lancet* 1986; i: 955.
2. Pak CYC, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. *Ann Intern Med* 1986; 104: 33–7.
3. Tekin A, *et al.* Oral potassium citrate treatment for idiopathic hypocitruria in children with calcium urolithiasis. *J Urol (Baltimore)* 2002; 168: 2572–4.
4. Pak CYC, *et al.* Prevention of stone formation and bone loss in absorptive hypercalciuria by combined dietary and pharmacological interventions. *J Urol (Baltimore)* 2003; 169: 465–9.

Adverse Effects and Treatment

Excessive use of bicarbonate or bicarbonate-forming compounds may lead to hypokalaemia and metabolic alkalosis, especially in patients with impaired renal function. Symptoms include mood changes, tiredness, slow breathing, muscle weakness, and irregular heartbeat. Muscle hypertonicity, twitching, and tetany may develop, especially in hypocalcaemic patients. Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium ions may be of particular importance.

Excessive doses of *sodium salts* may also lead to sodium overloading and hyperosmolality (see Adverse Effects of Sodium, p. 1795.2). Sodium bicarbonate given orally can cause stomach cramps, belching, and flatulence. Extravasation of irritant hypertonic sodium bicarbonate solutions resulting in local tissue necrosis has been reported after intravenous dosage.

Excessive doses of *potassium salts* may lead to hyperkalaemia (see Adverse Effects of Potassium, p. 1794.1). Ingestion of potassium salts can cause gastrointestinal adverse effects, and tablet formulations may cause contact irritation due to high local concentrations of potassium.

Excessive oral doses of *citrate salts* may have a laxative effect.

Effects on the gastrointestinal tract. In addition to minor gastrointestinal effects (see above), spontaneous rupture of the stomach, although an exceedingly rare event, has been reported on several occasions after ingestion of sodium bicarbonate. The bicarbonate was believed to have resulted in the rapid production of enough carbon dioxide to rupture a stomach already distended with food, liquid, or air.[1,2]

1. Mastrangelo MR, Moore EW. Spontaneous rupture of the stomach in a healthy adult man after sodium bicarbonate ingestion. *Ann Intern Med* 1984; 101: 649.
2. Lazebnik N, *et al.* Spontaneous rupture of the normal stomach after sodium bicarbonate ingestion. *J Clin Gastroenterol* 1986; 8: 454–6.

Effects on mental state. Sodium lactate infusions have been reported to induce panic attacks, especially in patients with anxiety states, and have been used as a pharmacological model in the evaluation of mechanisms involved in panic disorder.[1] However, the mechanism that underlies panic attacks induced by lactate remains unknown,[1] and it has been suggested[2] that rapid administration of the large sodium load may be involved. There has also been a report[3] of a patient receiving oral lactate (as calcium lactate) who was suffering from panic disorder associated with agoraphobia; when lactate was discontinued, the patient reported a reduction in panic intensity without a decrease in the frequency of attacks.

1. Bourin M, *et al.* Provocative agents in panic disorder. *Therapie* 1995; 50: 301–6.
2. Peskind ER, *et al.* Sodium lactate and hypertonic sodium chloride induce equivalent panic incidence, panic symptoms, and hypernatremia in panic disorder. *Biol Psychiatry* 1998; 44: 1007–16.
3. Robinson D, *et al.* Possible oral lactate exacerbation of panic disorder. *Ann Pharmacother* 1995; 29: 539–40.

Epileptogenic effect. Alkalosis may precipitate seizures; however, absence seizures have also been reported to be associated with sodium bicarbonate administration in a child in whom the serum pH was normal.[1]

1. Reif S, *et al.* Absence seizures associated with bicarbonate therapy and normal serum pH. *JAMA* 1989; 262: 1328–9.

Precautions

Bicarbonate or bicarbonate-forming compounds should not generally be given to patients with metabolic or respiratory alkalosis, hypocalcaemia, or hypochlorhydria. During treatment of acidosis, frequent monitoring of serum-electrolyte concentrations and acid–base status is essential.

Sodium-containing salts should be given extremely cautiously to patients with heart failure, oedema, renal impairment, hypertension, eclampsia, or aldosteronism (see Precautions for Sodium, p. 1795.3).

Potassium-containing salts should be given with considerable care to patients with renal or adrenocortical insufficiency, cardiac disease, or other conditions that may predispose to hyperkalaemia (see Precautions for Potassium, p. 1794.2).

Abuse. High doses of bicarbonate have been taken by athletes to enhance performance in endurance sports by buffering hydrogen ions produced in conjunction with lactic acid.[1] Bicarbonates have also been used to alkalinise the urine and prolong the half-life of basic drugs, notably sympathomimetics and stimulants, thereby avoiding detection; however, such a practice may enhance toxicity.

1. Kennedy M. Drugs and athletes—an update. *Adverse Drug React Bull* 1994; (Dec): 639–42.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium citrate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

The effect of oral bicarbonate or bicarbonate-forming compounds in raising intra-gastric pH may reduce or increase the rate and/or extent of absorption of a number of drugs (see also Antacids, p. 1803.1). Alkalinisation of the urine leads to increased renal clearance of acidic drugs such as salicylates, tetracyclines, and barbiturates. Conversely, it prolongs the half-life of basic drugs and may result in toxicity (see also under Abuse, above).

Sodium bicarbonate enhances lithium excretion. The use of *potassium-containing salts* with drugs that increase serum-potassium concentrations such as ACE inhibitors and potassium-sparing diuretics should generally be avoided (p. 1794.2). *Citrate salts* taken orally can enhance the absorption of aluminium from the gastrointestinal tract (see Toxicity, p. 1817.3 under Adverse Effects of Aluminium Hydroxide). Patients with impaired renal function are particularly susceptible to aluminium accumulation and citrate-containing oral preparations, including many effervescent or dispersible tablets, are best avoided by patients with renal failure taking aluminium-containing compounds.

Pharmacokinetics

Oral bicarbonate, such as sodium bicarbonate, neutralises gastric acid with the production of carbon dioxide. Bicarbonate not involved in that reaction is absorbed and in the absence of a deficit of bicarbonate in the plasma, bicarbonate ions are excreted in the urine, which is rendered alkaline, and there is an accompanying diuresis.

Acetates such as potassium acetate and sodium acetate, citrates such as potassium citrate, sodium acid citrate, and sodium citrate, and lactates such as sodium lactate are metabolised, after absorption, to bicarbonate.

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: LTK250; Urokit; *Austral.*: Chlorvescent; Sodibic; Urocit-K; *Austria*: Uralyt-U; *Belg.*: Natribic; Uralyt-U; *Braz.*: Litocit; *Canad.*: Bicart; Bromo Seltzer†; Cystoplus; Eno; Formula No 2K†; Hema BP-38; K-Citra; K-Lyte; Polycitra-K†; Urocit-K; *Chile*: Acalka†; Eucerin; *China*: Keweijia (可维加); Uralyt-U (友来特); *Cz.*: Uralyt-U; *Fin.*: Selutrio; *Fr.*: Bibag†; Hospasol; Soludial†; *Ger.*: Alkala T; Apocit; bicaNorm; Blanel; Kalitrans; Kalium; Kohlensaurebad Bastian; Nephrotrans; Uralyt-U; *Gr.*: Citrolithin; *Hong Kong*: Antacimin†; Citral†; Urocit-K; *Hung.*: Alkaligen; *India*: Adkalizer; Alkacool; Alkaline Citrate; Alkanil; Alkanorm; Alkaryl; Alkasol; Alkos; Allcitra; Ample; Cital; Citra; Citraglow; Citrakul; Citralka; Pulflo; Intalka; Jucitron; Metalka; Oricitral; *Irl.*: Cystopurin; Diarrest RF†; *Israel*: Al-Karish†; Babic†; Uralyt-U; *Ital.*: Citrosodina; Uralyt-U; *Jpn*: Meylon; *Malaysia*: Urocit-K; *Mex.*: Betsol Z; Bicarnat†; Debonal; *Neth.*: Citra-Lock; Hospasol; *Norw.*: Kajos; *NZ*: Citravescent†; *Philipp.*: Acalka; K-Cit; Zegacid; *Pol.*: Citrolyt; Litocid; *Port.*: Acalka; Alka-Seltzer; Extraneal; Hospasol; Uralyt-U; *Rus.*: Uralit-U (Уралит-У); *S.Afr.*: Crystacit; SB Gripe Water†; Uralyt-U; *Singapore*: Carrington's Gripe Water; Citral; Urocit-K; *Spain*: Acalka; Alka-Seltzer New Formula; Hospasol; Venofusin Bicarbonato; *Swed.*: Kajos; *Switz.*: Nephrotrans; Urocit; *Thai.*: Acalka; Arc-Soda; Carminative Medicine; Darbie; Sodamint Frx; Uralyt-U; *Turk.*: Anti-Asidoz; Parodontax; Urocit-K; *UK*: Boots Gripe Mixture 1 Month Plus; Canesten Oasis; Cymalon Cranberry; Cystitis Relief; Cystocalm; Cystopurin; SodiBic; *Ukr.*: Soda-Bufer (Сода-Буфер); Uralyt-U (Уралит-У); *USA*: Citra pH; K-Bicarb; K-Lyte; Neut; Urocit-K; *Venez.*: Policitra.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Ger.*: HanoOxygen E.

Pharmacopoeial Preparations

BP 2014: Alginate Raft-forming Oral Suspension; Alkaline Gentian Mixture; Aromatic Magnesium Carbonate Mixture; Compound Glucose, Sodium Chloride and Sodium Citrate Oral Solution; Compound Magnesium Trisilicate Oral Powder; Compound Sodium Bicarbonate Tablets; Compound Sodium Chloride Mouthwash; Compound Sodium Lactate Infusion; Kaolin and Morphine Mixture; Kaolin Mixture; Magnesium Trisilicate Mixture; Potassium Citrate Mixture; Sodium Bicarbonate Ear Drops; Sodium Bicarbonate Eye Lotion; Sodium Bicarbonate Infusion; Sodium Bicarbonate Oral Solution; Sodium Citrate Eye Drops; Sodium Citrate Irrigation Solution;

Sodium Lactate Infusion;
BPC 1968: Effervescent Potassium Tablets;
Ph. Eur.: Anticoagulant Acid-Citrate-Glucose Solutions (ACD); Anticoagulant Citrate-Phosphate-Glucose Solution (CPD);
USP 36: Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant Sodium Citrate Solution; Half-strength Lactated Ringer's and Dextrose Injection; Imipenem and Cilastatin for Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension; Magnesium Carbonate, Citric Acid, and Potassium Citrate for Oral Solution; PEG 3350 and Electrolytes for Oral Solution; Potassium and Sodium Bicarbonates and Citric Acid Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride Effervescent Tablets for Oral Solution; Potassium Bicarbonate and Potassium Chloride for Effervescent Oral Solution; Potassium Bicarbonate Effervescent Tablets for Oral Solution; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Potassium Chloride, Potassium Bicarbonate, and Potassium Citrate Effervescent Tablets for Oral Solution; Potassium Citrate And Citric Acid Oral Solution; Potassium Citrate Extended-release Tablets; Potassium Citrate Tablets; Potassium Gluconate and Potassium Citrate Oral Solution; Potassium Gluconate, Potassium Citrate, and Ammonium Chloride Oral Solution; Sodium Acetate Injection; Sodium Acetate Solution; Sodium Bicarbonate Injection; Sodium Bicarbonate Oral Powder; Sodium Bicarbonate Tablets; Sodium Citrate and Citric Acid Oral Solution; Sodium Lactate Injection; Sodium Lactate Solution; Tricitrates Oral Solution; Trikates Oral Solution.

Calcium

Calcio; Kalsiyum; Kalzium; Кальций.
Ca=40.078
UNII — SY7Q814VUP (calcium); 2M83C4R6ZB (calcium ion).

Description. Calcium is a cation given as various calcium-containing salts.

Incompatibility. Calcium salts have been reported to be incompatible with a wide range of drugs and parenteral mixtures containing, for example, phosphate. Complexes may form resulting in the formation of a precipitate.

References.
1. Newton DW, Driscoll DF. Calcium and phosphate compatibility: revisited again. *Am J Health-Syst Pharm* 2008; 65: 73–80.

Calcium Acetate

Acetate of Lime; Calcii Acetas; Calcio, acetato de; Calcium, acétate de; Calciumacetat; E263; Kalcio acetatas; Kalciumacetat; Kalcium-acetát; Kalsiumasetaatti; Kalsiyum Asetat; Lime Acetate; Ацетат Кальция; Уксуснокислый Кальций.
$C_4H_6CaO_4$=158.2
CAS — 62-54-4.
ATC — A12AA12.
ATC Vet — QA12AA12.
UNII — Y882YXF34X.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Calcium Acetate, Anhydrous). A white or almost white, hygroscopic powder. Freely soluble in water; slightly soluble in alcohol. A 5% solution in water has a pH of 7.2 to 8.2. Store in airtight containers.

USP 36: (Calcium Acetate). A white, odourless or almost odourless, hygroscopic, crystalline powder. It decomposes to calcium carbonate and acetone when heated to above 160 degrees. Freely soluble in water; slightly soluble in methyl alcohol; practically insoluble in dehydrated alcohol, in acetone, and in benzene. A 5% solution in water has a pH of 6.3 to 9.6. Store in airtight containers.

Equivalence. Each g of calcium acetate (anhydrous) represents about 6.3 mmol of calcium. Calcium acetate (anhydrous) 3.95 g is equivalent to about 1 g of calcium.

Calcium Chloride

Calcii Chloridum; Calcii chloridum dihydricum; Calcio, cloruro de; Calcium Chloratum; Calcium, chlorure de; Chlorid vápenatý; Cloreto de Cálcio; Cloruro cálcico; Cloruro de calcio; E509; Kalcio chloridas; Kalcium-klorid; Kalciumklorid; Kalsiumkloridi; Kalsiyum Klorür; Wapnia chlorek; Кальций Хлорид; Кальций Хлористый.
$CaCl_2$,xH_2O=110.0 (anhydrous); 147.0 (dihydrate)
CAS — 10043-52-4 (anhydrous calcium chloride); 7774-34-7 (calcium chloride hexahydrate); 10035-04-8 (calcium chloride dihydrate).
ATC — A12AA07; B05XA07; G04BA03.
ATC Vet — QA12AA07; QB05XA07; QG04BA03.
UNII — OFM21057LP (anhydrous calcium chloride); M4I0D6VV5M (calcium chloride dihydrate).

Pharmacopoeias. *Chin., Eur.* (see p. vii), *Jpn, US,* and *Viet.* include the dihydrate.

Eur. also specifies the hexahydrate.

Ph. Eur. 8: (Calcium Chloride Dihydrate; Calcii Chloridum Dihydricum). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Calcium Chloride Hexahydrate; Calcii Chloridum Hexahydricum). A white or almost white, crystalline mass or colourless crystals. Very soluble in water; freely soluble in alcohol. F.p. about 29 degrees.

USP 36: (Calcium Chloride). White, hard, odourless fragments or granules. Is deliquescent. Soluble 1 in 0.7 of water, 1 in 0.2 of boiling water, 1 in 4 of alcohol, and 1 in 2 of boiling alcohol. pH of a 5% solution in water is between 4.5 and 9.2. Store in airtight containers.

Equivalence. Each g of calcium chloride (dihydrate) represents about 6.8 mmol of calcium and 13.6 mmol of chloride. Calcium chloride (dihydrate) 3.67 g is equivalent to about 1 g of calcium.

Each g of calcium chloride (*hexahydrate*) represents about 4.56 mmol of calcium and 9.13 mmol of chloride. Calcium chloride (hexahydrate) 5.47 g is equivalent to about 1 g of calcium.

Calcium Citrate

Calcio, citrato de; Citrato tricálcico; Tricalcium Citrate; Лимоннокислый Кальций; Цитрат Кальция.
Tricalcium 2-hydroxypropane-1,2,3-tricarboxylate tetrahydrate.
$C_{12}H_{10}Ca_3O_{14}$,4H_2O=570.5
CAS — 5785-44-4.
UNII — MLM29U2X8S.

Pharmacopoeias. In *US.*

USP 36: (Calcium Citrate). A white, odourless, crystalline powder. Slightly soluble in water; insoluble in alcohol; freely soluble in diluted 3N hydrochloric acid and in diluted 2N nitric acid.

Equivalence. Each g of calcium citrate (tetrahydrate) represents about 5.3 mmol of calcium and 3.5 mmol of citrate. Calcium citrate (tetrahydrate) 4.74 g is equivalent to about 1 g of calcium.

Calcium Glubionate *(USAN, rINN)*

Calcii Glubionas; Calcio, glubionato de; Calcium Gluconate Lactobionate Monohydrate; Calcium Gluconogalactogluconate Monohydrate; Calcium Gluconolactobionate; Glubionate de Calcium; Glubionato de calcio; Кальция Глубионат.
Calcium D-gluconate lactobionate monohydrate.
$(C_{12}H_{21}O_{12})_2C_6H_{11}O_7Ca,H_2O$=610.5
CAS — 31959-85-0 (anhydrous calcium glubionate); 12569-38-9 (calcium glubionate monohydrate).
ATC — A12AA02.
ATC Vet — QA12AA02.
UNII — 3CF7K05D0Q.

Pharmacopoeias. *US* includes Calcium Glubionate Syrup.

Equivalence. Each g of calcium glubionate (monohydrate) represents about 1.6 mmol of calcium. Calcium glubionate (monohydrate) 15.2 g is equivalent to about 1 g of calcium.

Calcium Gluceptate

Calcii Glucoheptonas; Calcio, glucoheptonato de; Calcium Glucoheptonate (*pINN*); Calcium, glucoheptonate de; Calcium Glucosemonocarbonate; Calciumglucoheptonat; Gluceptato de calcio; Glucoheptonate de Calcium; Glucoheptonato de calcio; Kalcio gliukoheptonatas; Kalcium-glükoheptonát; Kalciumglükoheptonat; Kalcium-glukoheptonát; Kalsiumglukoheptonaatti; Кальция Глюкогептонат.
$C_{14}H_{26}CaO_{16}$=490.4
CAS — 17140-60-2 (anhydrous calcium gluceptate); 29039-00-7 (anhydrous calcium gluceptate).
ATC — A12AA10.
ATC Vet — QA12AA10.
UNII — L11651398J.

Pharmacopoeias. In *Eur.* (see p. vii). *US* allows anhydrous or with varying amounts of water of hydration.

Ph. Eur. 8: (Calcium Glucoheptonate). A mixture in variable proportions of calcium di(D-*glycero*-D-*gulo*-heptonate) and calcium di(D-*glycero*-D-*ido*-heptonate). A white or very slightly yellow, hygroscopic, amorphous powder. Very soluble in water; practically insoluble in alcohol and in acetone. A 10% solution in water has a pH of 6.0 to 8.0. Store in airtight containers.

USP 36: (Calcium Gluceptate). It is anhydrous or contains varying amounts of water of hydration. It consists of the calcium salt of the alpha-epimer of glucoheptonic acid or of a mixture of the alpha and beta epimers of glucoheptonic acid. A white to faintly yellow amorphous powder. It is stable in air, but the hydrous forms may lose part of their water of hydration on standing. Freely soluble in water; insoluble in alcohol and in many other organic solvents. pH of a 10% solution in water is between 6.0 and 8.0.

Equivalence. Each g of calcium gluceptate (anhydrous) represents about 2 mmol of calcium. Calcium gluceptate (anhydrous) 12.2 g is equivalent to about 1 g of calcium.

Calcium Gluconate

Calcii gluconas; Calcii Gluconas Monohydricus; Calcio, gluconato de; Calcium, gluconate de; Calcium Glyconate; Calciumgluconat; E578; Gluconato cálcico; Glukonan vápenatý monohydrát; Kalcio gliukonatas; Kalcium-glükonát; Kalciumglukonat; Kalsiumglukonaatti; Wapnia glukonian; Кальций Глюконат.
Calcium D-gluconate monohydrate.
$C_{12}H_{22}CaO_{14}H_2O$=448.4
CAS — 299-28-5 (anhydrous calcium gluconate); 18016-24-5 (calcium gluconate monohydrate).
ATC — A12AA03; D11AX03.
ATC Vet — QA12AA03; QD11AX03.
UNII — SQE6VB453K (calcium gluconate); CZN0M5R31 (calcium gluconate monohydrate).

Pharmacopoeias. In *Chin., Int., Jpn,* and *Viet.* Also in *Eur.* (see p. vii) and *US* as the anhydrous or the monohydrate form.

Calcium borogluconate is included as an injection in *BP (Vet).*

Ph. Eur. 8: (Calcium Gluconate). A white or almost white, crystalline or granular, powder. Sparingly soluble in water; freely soluble in boiling water.

Ph. Eur. 8: (Calcium Gluconate, Anhydrous). A white or almost white, crystalline, or granular powder. Sparingly soluble in water; freely soluble in boiling water.

USP 36: (Calcium Gluconate). It is anhydrous or contains one molecule of water of hydration. White, odourless, crystalline granules or powder. Slowly soluble 1 in 30 of water; soluble 1 in 5 of boiling water; insoluble in alcohol. Its solutions are neutral to litmus.

Equivalence. Each g of calcium gluconate (monohydrate) represents about 2.2 mmol of calcium. Calcium gluconate (monohydrate) 11.2 g is equivalent to about 1 g of calcium.

Calcium Glycerophosphate

Calcii Glycerophosphas; Calcio, glicerofosfato de; Calcium Glycerinophosphate; Calcium, glycérophosphate de; Calcium Glycerylphosphate; Calciumglycerophosphat; Glicerofosfato cálcico; Glycerofosforečnan vápenatý; Kalcio glicerofosfatas; Kalcium-glicerofoszfát; Kalciumglycerofosfat; Kalsiumglyserofosfaatti; Кальций Глицерофосфат.
$C_3H_7CaO_6P$,xH_2O=210.1 (anhydrous)
CAS — 27214-00-2 (anhydrous calcium glycerophosphate).
ATC — A12AA08.
ATC Vet — QA12AA08.
UNII — XWV9Z12C1C.

Pharmacopoeias. In *Eur.* (see p. vii), *US.*, and *Viet.*

Ph. Eur. 8: (Calcium Glycerophosphate). A mixture in variable proportions of calcium (*RS*)-2,3-dihydroxypropyl phosphate and of calcium 2-hydroxy-1-(hydroxymethyl) ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. A white or almost white, hygroscopic powder. Sparingly soluble in water; practically insoluble in alcohol. It loses not more than 12% of its weight on drying.

USP 36: (Calcium Glycerophosphate). A mixture, in variable proportions, of calcium (*RS*)-2,3-dihydroxypropyl phosphate and calcium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate, which may be hydrated. It contains not less than 18.6% and not more than 19.4% of calcium, calculated with reference to the dried substance. Store at a temperature between 20 degrees and 25 degrees, excursions permitted between 15 degrees and 30 degrees.

Equivalence. Each g of calcium glycerophosphate (anhydrous) represents about 4.8 mmol of calcium. Calcium glycerophosphate (anhydrous) 5.24 g is equivalent to about 1 g of calcium.

Calcium Hydrogen Phosphate

Calcii et Hydrogenii Phosphas; Calcii Hydrogenophosphas; Calcio, hidrogenofosfato de; Calcium, hydrogénophosphate

de; Calcium Hydrophosphoricum; Calcium Monohydrogen Phosphate; Dibasic Calcium Phosphate; Dicalcium Orthophosphate; Dicalcium Phosphate; E341; Fosfato dibásico de calcio; Hydrogenfosforečnan vápenatý; Kalcio-vandenilio fosfatas; Kalcium-hidrogén-foszfát; Kalciumvätefosfat; Kalsiumvetyfosfaatti; Wapnia wodorofosforan; Ортофосфат Кальция Двузамещенный; Дикальций фосфат.

Calcium hydrogen orthophosphate.

$CaHPO_4$=136.1 (anhydrous); 172.1 (dihydrate)

CAS — 7757-93-9 (anhydrous calcium hydrogen phosphate); 7789-77-7 (calcium hydrogen phosphate dihydrate).

UNII — L11K75P92J (anhydrous calcium hydrogen phosphate); O7TSZ97GEP (calcium hydrogen phosphate dihydrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Int., Jpn,* and *US,* which includes monographs for the anhydrous substance and the dihydrate form.

Ph. Eur. 8: (Calcium Hydrogen Phosphate, Anhydrous; Calcii Hydrogenophosphas Anhydricus). A white or almost white, crystalline powder. Practically insoluble in water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.

Ph. Eur. 8: (Calcium Hydrogen Phosphate Dihydrate; Calcii Hydrogenophosphas Dihydricus; Calcium Hydrogen Phosphate BP 2014). A white or almost white, crystalline powder. Practically insoluble in cold water and in alcohol; dissolves in dilute hydrochloric acid and in dilute nitric acid.

The BP 2014 gives Dibasic Calcium Phosphate as an approved synonym.

USP 36: (Anhydrous Dibasic Calcium Phosphate).

USP 36: (Dibasic Calcium Phosphate Dihydrate).

Equivalence. Each g of calcium hydrogen phosphate (dihydrate) represents about 5.8 mmol of calcium and of phosphate. Calcium hydrogen phosphate (dihydrate) 4.29 g is equivalent to about 1 g of calcium.

Calcium Lactate

Calcii Lactas; Calcio, lactato de; Calcium, lactate de; E327; Kalcio laktatas; Kalciumlaktat; Kalcium-laktát; Kalsiumlaktaatti; Kalsiyum Laktat; Lactato cálcico; Mléčnan vápenatý; Wapnia mleczan; Лактат Кальция; Молочнокислый Кальций.

Calcium 2-hydroxypropionate.

$C_6H_{10}CaO_6.xH_2O$=218.2 (anhydrous); 308.3 (pentahydrate); 272.3(trihydrate)

CAS — 814-80-2 (anhydrous calcium lactate); 41372-22-9 (hydrated calcium lactate); 5743-47-5 (calcium lactate pentahydrate); 63690-56-2 (calcium lactate pentahydrate).

ATC — A12AA05.

ATC Vet — QA12AA05.

UNII — 2URQ2N32W3 (anhydrous calcium lactate); 4FM1N296CM (calcium lactate pentahydrate).

Pharmacopoeias. In *Chin., Eur.* (see p. vii), *Jpn,* and *US.*

Eur. has separate monographs for the anhydrous substance, the monohydrate, the pentahydrate, and the trihydrate. *US* allows anhydrous or hydrous forms. *Viet.* has monographs for the pentahydrate and the trihydrate.

Ph. Eur. 8: (Calcium Lactate, Anhydrous; Calcii Lactas Anhydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

Ph. Eur. 8: (Calcium Lactate Monohydrate; Calcii Lactas Monohydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

Ph. Eur. 8: (Calcium Lactate Pentahydrate; Calcii Lactas Pentahydricus). A white or almost white, slightly efflorescent, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

The BP 2014 gives Calcium Lactate as an approved synonym.

Ph. Eur. 8: (Calcium Lactate Trihydrate; Calcii Lactas Trihydricus). A white or almost white, crystalline or granular powder. Soluble in water; freely soluble in boiling water; very slightly soluble in alcohol.

USP 36: (Calcium Lactate). White, practically odourless, granules or powder. The pentahydrate is somewhat efflorescent and at 120 degrees becomes anhydrous. The pentahydrate is soluble 1 in 20 of water and practically insoluble in alcohol. Store in airtight containers.

Equivalence. Each g of calcium lactate (trihydrate) represents about 3.7 mmol of calcium. Each g of calcium lactate (pentahydrate) represents about 3.2 mmol of calcium. Calcium lactate (pentahydrate) 7.7 g and calcium lactate (trihydrate) 6.8 g are each equivalent to about 1 g of calcium.

Calcium Lactate Gluconate

Calcio, gluconato lactato de; Calcium Gluconolactate.

$Ca_5(C_3H_5O_3)_6(C_6H_{11}O_7)_4.2H_2O$=1551.4

CAS — 11116-97-5.

ATC — A12AA06.

ATC Vet — QA12AA06.

UNII — 472LWJ3Y9N.

Equivalence. Each g of calcium lactate gluconate (dihydrate) represents about 3.2 mmol of calcium. Calcium lactate gluconate (dihydrate) 7.74 g is equivalent to about 1 g of calcium.

Calcium Lactobionate

Calcii Lactobionas; Calcio, lactobionato de; Calcium Lactobionate Dihydrate; Kalciumlaktobionat; Kalsiumlaktobionaatti; Lactobionato cálcico dihidrato; Кальция Лактобионат.

Calcium 4-*O*-β-D-galactopyranosyl-D-gluconate dihydrate.

$C_{24}H_{42}CaO_{24}.2H_2O$=790.7

CAS — 110638-68-1.

UNII — 7D8YVA497F.

Pharmacopoeias. In *US.*

USP 36: (Calcium Lactobionate). pH of a 5% solution in water is between 5.4 and 7.4.

Equivalence. Each g of calcium lactobionate (dihydrate) represents about 1.3 mmol of calcium. Calcium lactobionate (dihydrate) 19.7 g is equivalent to about 1 g of calcium.

Calcium Levulinate *(BAN)*

Calcii Laevulas; Calcii Laevulinas; Calcii Laevulinas Dihydricus; Calcii Levulinas Dihydricum; Calcio, levulinato de; Calcium Laevulate; Calcium Laevulinate; Calcium, lévulinate de; Kalcio levulinatas; Kalciumlevulat; Kalcium-levulát dihydrát; Kalciumlevulinat; Kalcium-levulinát; Kalsiumlevulaatti; Kalsiumlevulinaatti; Lévulinate Calcique; Levulinato cálcico dihidrato; Кальция Левулат.

Calcium 4-oxovalerate dihydrate.

$C_{10}H_{14}CaO_6.2H_2O$=306.3

CAS — 591-64-0 (anhydrous calcium levulinate); 5743-49-7 (calcium levulinate dihydrate).

ATC — A12AA30.

ATC Vet — QA12AA30.

UNII — T6133SO781.

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Calcium Levulinate Dihydrate). A white or almost white, crystalline powder. Freely soluble in water; very slightly soluble in alcohol; practically insoluble in dichloromethane. A 10% solution in water has a pH of 6.8 to 7.8. Protect from light.

USP 36: (Calcium Levulinate). A white crystalline or amorphous powder, having a faint odour suggestive of burnt sugar. Freely soluble in water; slightly soluble in alcohol; insoluble in chloroform and in ether. pH of a 10% solution in water is between 7.0 and 8.5.

Equivalence. Each g of calcium levulinate (dihydrate) represents about 3.3 mmol of calcium. Calcium levulinate (dihydrate) 7.64 g is equivalent to about 1 g of calcium.

Calcium Phosphate

Calcii Phosphas; Calcio, fosfato de; Calcium Orthophosphate; E341; Fosfato Tricalcico; Fosfato Tricálcico; Fosforečnan vápenatý; Kalcio fosfatas; Kalcium-foszfát; Phosphate Tertiaire de Calcium; Phosphate tricalcique; Precipitated Calcium Phosphate; Tricalcii Phosphas; Tricalcium Phosphate; Tricalciumphosphat; Trikalciumfosfat; Trikalsiumfosfaatti; Wapnia fosforan; Ортофосфат Кальция Трёхзамещенный.

CAS — 7758-87-4 (tricalcium diorthophosphate); 12167-74-7 (calcium hydroxide phosphate).

ATC — A12AA01.

ATC Vet — QA12AA01.

UNII — 97Z1WI3NDX (calcium phosphate); K4C08XP666 (tricalcium diorthophosphate).

Description. Calcium phosphate is not a clearly defined chemical entity but is a mixture of calcium phosphates that has been most frequently described as either tricalcium diorthophosphate, $Ca_3(PO_4)_2$ = 310.2, or calcium hydroxide phosphate, $Ca_5OH(PO_4)_3$ = 502.3.

Pharmacopoeias. In *Eur.* (see p. vii), *Int.,* and *Viet.* Also in *USNF.*

Br. also includes a form for homoeopathic preparations.

Ph. Eur. 8: (Calcium Phosphate). It consists of a mixture of calcium phosphates and contains 35 to 40% of Ca. A white or almost white powder. Practically insoluble in water; dissolves in dilute hydrochloric acid and in dilute nitric acid.

The BP 2014 gives Tribasic Calcium Phosphate as an approved synonym.

USNF 31: (Tribasic Calcium Phosphate). It consists of a variable mixture of calcium phosphates having the approximate composition $10CaO.3P_2O_5.H_2O$. It contains not less than 34% and not more than 40% of calcium. A white, odourless, powder. Practically insoluble in water; insoluble in alcohol; readily soluble in 3N hydrochloric acid and in 2N nitric acid.

BP 2014: (Calcium Phosphate for Homoeopathic Preparations; Calcium Phosphoricum for Homoeopathic Preparations).

Calcium Pidolate *(pINNM)*

Calcii Pidolas; Calcio, pidolato de; Calcium Pyroglutamate; Pidolate de Calcium; Pidolato cálcico; Pidolato de calcio; Кальций Пидолат.

Calcium 5-oxopyrrolidine-2-carboxylate.

$Ca(C_5H_6NO_3)_2$=296.3

CAS — 31377-05-6.

UNII — 7Y2LVU5EKK.

Equivalence. Each g of calcium pidolate (anhydrous) represents about 3.4 mmol of calcium. Calcium pidolate (anhydrous) 7.39 g is equivalent to about 1 g of calcium.

Calcium Silicate

Calcio, silicato de; E552; Silicato cálcico; Кремнекислый Кальций; Силикат Кальция.

CAS — 1344-95-2; 10101-39-0 (calcium metasilicate); 10034-77-2 (calcium diorthosilicate); 12168-85-3 (calcium trisilicate).

ATC — A02AC02.

ATC Vet — QA02AC02.

UNII — S4255P4G5M.

Description. A naturally occurring mineral, the most common forms being calcium metasilicate ($CaSiO_3$ = 116.2), calcium diorthosilicate (Ca_2SiO_4 = 172.2), and calcium trisilicate (Ca_3SiO_5 = 228.3). It is usually found in hydrated forms containing various amounts of water of crystallisation. Commercial calcium silicate is prepared synthetically.

Pharmacopoeias. In *USNF.*

USNF 31: (Calcium Silicate). Crystalline or amorphous calcium silicate is a compound of calcium oxide and silicon dioxide containing not less than 4% of CaO and not less than 35% of SiO_2. A white to off-white free-flowing powder. Insoluble in water; with mineral acids it forms a gel. A 5% aqueous suspension has a pH of 8.4 to 11.2.

Calcium Sodium Lactate

Calcio, lactato sódico de.

$2C_3H_5NaO_3.(C_3H_5O_3)_2Ca.4H_2O$=514.4

Equivalence. Each g of calcium sodium lactate (tetrahydrate) represents about 1.9 mmol of calcium and 3.9 mmol of sodium and of lactate. Calcium sodium lactate (tetrahydrate) 12.8 g is equivalent to about 1 g of calcium.

Uses and Administration

Calcium salts are used in the management of **hypocalcaemia** (p. 1776.2) and **calcium deficiency states** resulting from dietary deficiency or ageing (see also Osteoporosis, p. 1168.1). Doses may be expressed in terms of mmol or mEq of calcium, mass (mg) of calcium, or mass of calcium salt (for comparative purposes, see Table 1, p. 1785).

In simple deficiency states calcium salts may be given orally, usually in doses of 10 to 50 mmol (400 mg to 2 g) of calcium daily adjusted to the individual patient's requirements.

In severe acute hypocalcaemia or hypocalcaemic tetany parenteral dosage is necessary, generally by slow intravenous injection or continuous infusion of calcium chloride or calcium gluconate (see also Administration, p. 1785.2). A typical dose is 2.25 to 4.5 mmol of calcium by slow intravenous injection. This may be repeated as required, or followed by continuous intravenous infusion. One suggested regimen for infusion is 22.5 mmol of calcium as calcium gluconate in 1 litre of infusion solution, given at an initial rate of 50 mL/hour. Plasma-calcium may be monitored every 4 to 6 hours and the dose adjusted accordingly. About 2.25 mmol of calcium is provided by 10 mL of calcium gluconate 10%. Calcium gluceptate and calcium glycerophosphate with calcium lactate have been given by the intramuscular route; the chloride and

Table 1. Some calcium salts and their calcium content.

Calcium salt	Calcium content per g		
	mg	mmol	mEq
Calcium acetate (anhydrous)	253	6.3	12.6
Calcium carbonate	400	10.0	20.0
Calcium chloride (dihydrate)	273	6.8	13.6
Calcium chloride (hexahydrate)	183	4.6	9.1
Calcium citrate (tetrahydrate)	211	5.3	10.5
Calcium glubionate (monohydrate)	66	1.6	3.3
Calcium gluceptate (anhydrous)	82	2.0	4.1
Calcium gluconate (monohydrate)	89	2.2	4.5
Calcium glycerophosphate (anhydrous)	191	4.8	9.5
Calcium hydrogen phosphate (dihydrate)	233	5.8	11.6
Calcium lactate (anhydrous)	184	4.6	9.2
Calcium lactate (trihydrate)	147	3.7	7.3
Calcium lactate (pentahydrate)	130	3.2	6.5
Calcium lactate gluconate (dihydrate)	129	3.2	6.4
Calcium lactobionate (dihydrate)	51	1.3	2.5
Calcium levulinate (dihydrate)	131	3.3	6.5
Calcium phosphate [$10CaO.3P_2O_5.H_2O$]	399	10.0	19.9
Calcium pidolate (anhydrous)	135	3.4	6.7
Calcium silicate [$CaSiO_3$]	345	8.6	17.2
Calcium sodium lactate (tetrahydrate)	78	1.9	3.9

gluconate are unsuitable for this route because of their irritancy.

Intravenous calcium salts are also used to reverse the toxic cardiac effects of potassium in the emergency treatment of severe **hyperkalaemia** (p. 1777.1), and as an antidote to magnesium in severe **hypermagnesaemia** (p. 1776.2). For these indications, 2.25 to 4.5 mmol of calcium (10 to 20 mL of calcium gluconate 10%) is commonly used.

Individual calcium salts have specific uses. Calcium carbonate (p. 1824.3) or acetate are effective phosphate binders and are given orally to reduce phosphate absorption from the gut in patients with **hyperphosphataemia**; this is particularly relevant to patients with chronic renal failure in order to prevent the development of renal osteodystrophy (p. 1170.1). Doses are adjusted according to serum phosphate concentrations. Typical oral doses of calcium carbonate range from about 3 to 7 g (1.2 to 2.8 g calcium) daily in divided doses. Usual oral doses of calcium acetate are about 4 to 8 g (1 to 2 g calcium) daily in divided doses; a daily maximum of calcium acetate 12 g (3 g calcium) has been recommended. However, the US National Kidney Foundation suggests that the total dose of elemental calcium provided by the calcium-based phosphate binder should not exceed 1.5 g daily in those with kidney failure.

Calcium carbonate and calcium silicate, given orally, are used for their **antacid** properties (p. 1803.1). A supersaturated calcium phosphate solution is used topically as a mouthwash to manage conditions such as **dry mouth** (p. 2175.3) and **mucositis** associated with chemotherapy or radiotherapy (p. 732.1).

Some of the calcium salts discussed here also have *pharmaceutical uses* as diluents in capsules and tablets, buffers and dissolution aids in dispersible tablets, disintegrant and anticaking agents, and as a basis or abrasive in dental preparations. Calcium phosphate is also used as a bone graft substitute.

Homoeopathy

Various calcium salts have been used in homoeopathic medicines under the following names:

- Calcium acetate: Calcarea acetica; Calc acet; Calc. ace.
- Calcium arsenite: Calcium arsenicosum; Calcarea arsenicosa; Cal. ars.
- Calcium chloride: Calcarea muriatica; Cal. mur.; Calc mur
- Calcium hydrogen phosphate: Calcium phosphoricum
- Calcium lactate: Calcarea lactica; Calc lac
- Calcium oxalate: Calcarea oxalica; Cal. oxal.; Calc oxal
- Calcium phosphate: Calcarea phosphorica; Calc. phos.; Cal. phos.
- Calcium silicate: Calcarea silicata; Calc. sil.

Other calcium salts used in homoeopathy and described elsewhere include: calcium bromide (p. 2461.1), calcium carbonate (p. 1824.3), calcium fluoride (p. 2053.1), calcium hydroxide (p. 2465.1), calcium hypophosphite (p. 2530.3), calcium iodide (p. 1658.1), and calcium sulfate (p. 2173.1).

Administration. Some prefer calcium chloride to calcium gluconate for parenteral preparations,[1,2] because retention of the chloride is greater and more predictable than of the gluconate, and results in a more predictable increase in extracellular ionised calcium concentration. However, calcium chloride is considered to be the most irritant of the calcium salts in general use (see Adverse Effects, p. 1786.1).

Calcium gluconate has been given by the intraperitoneal route[3] for the treatment of chronic hypocalcaemia after parathyroidectomy in a patient undergoing continuous ambulatory peritoneal dialysis, resulting in improved systemic bioavailability compared with oral and intravenous use.

1. Worthley LIG, Phillips PJ. Intravenous calcium salts. *Lancet* 1980; **ii**: 149.
2. Broner CW, *et al.* A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr* 1990; **117**: 986–9.
3. Stamatakis MK, Seth SK. Treatment of chronic hypocalcemia with intraperitoneal calcium. *Am J Health-Syst Pharm* 1995; **52**: 201–3.

Bites and stings. Calcium gluconate 10% solution has been given intravenously as an alternative to the use of conventional muscle relaxants for the management of pain and muscle spasm associated with neurotoxic spider envenomation (p. 2420.1) by species such as *Latrodectus mactans* (black widow spider).[1,2] Although the precise mechanism of action of calcium in the alleviation of neuromuscular symptoms is unknown it is believed to be due to the replenishment of calcium stores in the sarcoplasmic reticulum of muscle depleted by stimulation.

1. Binder LS. Acute arthropod envenomation: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; **4**: 163–73.
2. Woestman R, *et al.* The black widow: is she deadly to children? *Pediatr Emerg Care* 1996; **12**: 360–4.

Bone disease. Calcium is essential for the development and maintenance of normal bone, and calcium salts may be indicated in the treatment of some bone disorders associated with calcium deficiency, such as certain types of osteomalacia and rickets (p. 1168.1). Oral doses of 1 to 3 g of calcium daily are used in osteomalacia.

Oral calcium supplements can also be used as an adjunct in the management of osteoporosis (p. 1168.1) and corticosteroid-induced osteoporosis (see Effects on Bones and Joints, under Corticosteroids, p. 1616.2).

Cramps. Calcium salts are one of a number of interventions that have been tried in the management of cramps (see Muscle Spasm, p. 2014.1). However, evidence for these interventions is mostly lacking and a small systematic review concluded that oral calcium was not of benefit for leg cramps during pregnancy.[1]

1. Young G, Jewell D. Interventions for leg cramps in pregnancy. Available in The Cochrane Database of Systematic Reviews; Issue 1, Chichester: John Wiley; 2002 (accessed 21/06/05).

Diagnosis of insulinoma. Calcium stimulates the release of insulin from insulinomas (see Neuroendocrine Tumours, p. 716.3). Intra-arterial calcium gluconate, followed by hepatic venous sampling, has been found to be accurate and sensitive in the diagnosis and localisation of insulinomas,[1-4] even when other investigations have been negative.[3,6]

1. Doppman JL, *et al.* Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med* 1995; **123**: 269–73.
2. Lo CY, *et al.* Value of intra-arterial calcium stimulated venous sampling for regionalization of pancreatic insulinomas. *Surgery* 2000; **128**: 903–9.
3. Brändle M, *et al.* Assessment of selective arterial calcium stimulation and hepatic venous sampling to localize insulin-secreting tumours. *Clin Endocrinol (Oxf)* 2001; **55**: 357–62.
4. Grant CS. Insulinoma. *Best Pract Res Clin Gastroenterol* 2005; **19**: 783–98.
5. O'Shea D, *et al.* Localization of insulinomas by selective intraarterial calcium injection. *J Clin Endocrinol Metab* 1996; **81**: 1623–7.
6. Pereira PL, *et al.* Insulinoma and islet cell hyperplasia: value of the calcium intraarterial stimulation test when findings of other preoperative studies are negative. *Radiology* 1998; **206**: 703–9.

Fluoride toxicity. Inorganic fluoride is corrosive to skin and mucous membranes and acute intoxication disrupts many physiological systems; severe burns and profound hypocalcaemia may ensue. Absorption of the fluoride can be prevented by conversion to an insoluble form such as calcium fluoride and thus irrigation of skin (or gastric lavage as appropriate) with lime water, milk, or a 1% solution of calcium gluconate is recommended. Immediate treatment should also consist of 10 mL of calcium gluconate 10% intravenously, repeated after one hour; 30 mL should be given if tetany is present. In the short term affected skin and tissue should be injected with a 10% solution of calcium gluconate at a dose of 0.5 mL/cm² and burnt skin treated with a calcium gluconate 2.5% gel.[1]

See also under Hydrofluoric Acid, p. 2529.2.

1. McIvor ME. Acute fluoride toxicity: pathophysiology and management. *Drug Safety* 1990; **5**: 79–85.

Hypertension. Meta-analysis suggests that calcium supplementation results in a small reduction in both systolic and diastolic blood pressure,[1] or in systolic blood pressure alone.[2] However, the effect was too small to support the use of calcium supplementation for preventing or treating hypertension (p. 1251.1). The poor quality of the studies and the heterogeneity between them was also commented on.[2] In a controlled study, calcium with vitamin D supplementation reduced systolic blood pressure more effectively than calcium alone.[3]

1. Griffith LE, *et al.* The influence of dietary and nondietary calcium supplementation on blood pressure: an updated metaanalysis of randomized controlled trials. *Am J Hypertens* 1999; **12**: 84–92.
2. Dickinson HO, *et al.* Calcium supplementation for the management of primary hypertension in adults. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2006 (accessed 06/03/09).
3. Pfeifer M, *et al.* Effects of a short-term vitamin D$_3$ and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. *J Clin Endocrinol Metab* 2001; **86**: 1633–7.

PREGNANCY. Despite an earlier meta-analysis[1] which concluded that calcium supplementation during pregnancy reduced systolic and diastolic blood pressure and the incidence of pre-eclampsia and hypertension, results from a double-blind, placebo-controlled study in a total of 4589 women indicated that calcium supplementation during normal pregnancy did not prevent pre-eclampsia, pregnancy-associated hypertension without pre-eclampsia, or a number of other related disorders.[2] A subsequent review[3] found that calcium supplementation was beneficial, but it was noted that there was a wide variation in results between different studies; most of the effect was in studies including women identified as being at high risk for pre-eclampsia, and results from studies including lower-risk women found that calcium had no effect. The high-risk studies were carried out in areas with a low dietary calcium intake, suggesting that benefit might be greatest in such populations. However, a further study[4] in 8325 women living in areas with a low calcium intake but not specifically at high risk found that calcium supplementation had no significant effect on the incidence of pre-eclampsia, although it did reduce the risk of severe pre-eclamptic complications. An updated meta-analysis,[5] which included this study, concluded that calcium supplementation during pregnancy was safe and that it did reduce the incidence of pre-eclampsia and serious complications, particularly in high-risk women.

For discussions of hypertension in pregnancy and eclampsia and pre-eclampsia, see p. 1251.1 and p. 511.1, respectively.

1. Bucher HC, *et al.* Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials. *JAMA* 1996; **275**: 1113–17. Correction. *ibid.*; **276**: 1388.
2. Levine RJ, *et al.* Trial of calcium to prevent preeclampsia. *N Engl J Med* 1997; **337**: 69–76.
3. DerSimonian R, Levine RJ. Resolving discrepancies between a meta-analysis and a subsequent large controlled trial. *JAMA* 1999; **282**: 664–70.
4. Villar J, *et al.* World Health Organization Calcium Supplementation for the Prevention of Preeclampsia Trial Group. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. *Am J Obstet Gynecol* 2006; **194**: 639–49.
5. Hofmeyr GJ, *et al.* Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Available in The Cochrane Database of Systematic Reviews: Issue 8. Chichester: John Wiley; 2010 (accessed 20/08/10).

Malignant neoplasms. There is some evidence that calcium supplementation may modestly reduce the risk[1-3] of colorectal cancer and its recurrence (p. 707.2).[4-6] This protective effect appears to be more pronounced for advanced colorectal lesions,[7] and when serum concentrations of vitamin D are in the higher range.[8]

1. Wu K, *et al.* Calcium intake and risk of colon cancer in women and men. *J Natl Cancer Inst* 2002; **94**: 437–46.
2. McCullough ML, *et al.* Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States). *Cancer Causes Control* 2003; **14**: 1–12.
3. Cho E, *et al.* Dairy foods, calcium, and colorectal cancer: a pooled analysis of 10 cohort studies. *J Natl Cancer Inst* 2004; **96**: 1015–22. Correction. *ibid.*; 1724.
4. Baron JA, *et al.* Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999; **340**: 101–7.
5. Bonithon-Kopp C, *et al.* Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. *Lancet* 2000; **356**: 1300–6.
6. Martínez ME, *et al.* Calcium, vitamin D, and risk of adenoma recurrence (United States). *Cancer Causes Control* 2002; **13**: 213–20.
7. Wallace K, *et al.* Effect of calcium supplementation on the risk of large bowel polyps. *J Natl Cancer Inst* 2004; **96**: 921–5.
8. Grau MV, *et al.* Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. *J Natl Cancer Inst* 2003; **95**: 1765–71.

Premenstrual syndrome. Calcium supplementation was effective in relieving the luteal phase symptoms of premenstrual syndrome (p. 2272.3) in 1 study.[1] A review of this and other studies suggested that calcium supplementation at a dose of 1.2 to 1.6 g daily should be considered in patients with premenstrual syndrome.[2]

1. Thys-Jacobs S, *et al.* Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol* 1998; **179**: 444–52.
2. Ward MW, Holimon TD. Calcium treatment for premenstrual syndrome. *Ann Pharmacother* 1999; **33**: 1356–8.

Adverse Effects and Treatment

Oral calcium salts can cause gastrointestinal irritation; calcium chloride is generally considered to be the most irritant of the commonly used calcium salts.

Injection of calcium salts can also produce irritation, and intramuscular or subcutaneous injection in particular can cause local reactions including sloughing or necrosis of the skin; solutions of calcium chloride are extremely irritant and should not be injected intramuscularly or subcutaneously. Soft-tissue calcification has followed the use of calcium salts parenterally.

Excessive amounts of calcium salts may lead to hypercalcaemia. This complication is usually associated with parenteral use, but can occur after oral dosage, usually in patients with renal failure or who are also taking vitamin D. Symptoms of hypercalcaemia include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac arrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to symptoms of hypercalcaemia, as well as a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcaemia will usually resolve if calcium and other contributory drugs such as vitamin D are stopped (see also Vitamin D-mediated Hypercalcaemia, p. 1776.1). If hypercalcaemia is severe, urgent treatment is required as outlined on p. 1776.1.

Effects on the cardiovascular system. The results of a meta-analysis suggested that the use of oral calcium supplements alone (without vitamin D) might be associated with an increased risk of myocardial infarction.[1] However, none of the 15 included studies had cardiovascular outcomes as primary end-points, and collection of the data on cardiovascular events was not standardised. Also, the results of this analysis may not apply to the use of calcium supplements with vitamin D, which is generally recommended in the treatment and prevention of osteoporosis (p. 1168.1).

1. Bolland MJ, *et al.* Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; 341: 289. Full version: http://www.bmj.com/cgi/reprint/341/jul29_1/c3691 (accessed 18/08/10)

Precautions

Solutions of calcium salts, particularly calcium chloride, are irritant, and care should be taken to prevent extravasation during intravenous injection. Calcium salts should be given cautiously to patients with renal impairment, or diseases associated with hypercalcaemia such as sarcoidosis and some malignancies. In addition, they should generally be avoided in patients with calcium renal calculi, or a history of renal calculi. Calcium chloride, because of its acidifying nature, is unsuitable for the treatment of hypocalcaemia caused by renal insufficiency or in patients with respiratory acidosis or failure.

Plasma-calcium concentrations should be monitored closely in patients with renal impairment and during parenteral dosage and if large doses of vitamin D are used concurrently.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies calcium glubionate and calcium lactate gluconate as not porphyrinogenic: they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Hypercalcaemia has occurred when calcium salts are given with thiazide diuretics or vitamin D. Vitamin D increases the gastrointestinal absorption of calcium and thiazide diuretics decrease its urinary excretion. Plasma-calcium concentrations should be monitored in patients receiving the drugs together.

Bran decreases the gastrointestinal absorption of calcium, and may therefore decrease the efficacy of calcium supplements. Corticosteroids also reduce calcium absorption.

Calcium enhances the effects of digitalis glycosides on the heart and may precipitate digitalis intoxication; parenteral calcium therapy is best avoided in patients receiving cardiac glycosides. Citrate salts increase the absorption of aluminium from the gastrointestinal tract (see Toxicity, under Adverse Effects of Aluminium Hydroxide, p. 1817.3), therefore patients with renal failure taking aluminium compounds should avoid taking calcium citrate. Calcium salts reduce the absorption of a number of other drugs such as bisphosphonates, fluoride, some fluoroquinolones, and tetracyclines; doses should be separated by at least 3 hours.

Pharmacokinetics

Calcium is absorbed mainly from the small intestine by active transport and passive diffusion. About one-third of ingested calcium is absorbed although this can vary depending upon dietary factors and the state of the small intestine; also absorption is increased in calcium deficiency and during periods of high physiological requirement such as during childhood or pregnancy and lactation. 1,25-Dihydroxycholecalciferol (calcitriol), a metabolite of vitamin D, enhances the active phase of absorption.

Excess calcium is mainly excreted renally. Unabsorbed calcium is eliminated in the faeces, together with that secreted in the bile and pancreatic juice. Minor amounts are lost in the sweat, skin, hair, and nails. Calcium crosses the placenta and is distributed into breast milk.

Human Requirements

Calcium is the most abundant mineral in the body and is an essential body electrolyte. However, defining individual calcium requirements has proved difficult and guidelines vary widely by country and culture. Some authorities have adopted a factorial approach. For example, in the UK the dietary reference value (DRV) represents the apparent calcium requirements of healthy people under the prevailing dietary circumstances. The amount of calcium absorbed varies according to several factors including the requirements of the body, but is normally only about 30 to 40% of the dietary intake.

The richest dietary sources of calcium are milk and milk products. Significant amounts can also be consumed in green leafy vegetables, fortified flour, the soft bones of fish, and hard water.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1) have been published for calcium.[1] In the USA recommended dietary allowances (RDA) had been set,[2] but have been replaced by dietary reference intakes (see p. 2046.1).[3] In the UK the estimated average requirement (EAR) for adults is 525 mg (13.1 mmol) daily and the reference nutrient intake (RNI) for adults is 700 mg (17.5 mmol) daily; these figures are based on a mean absorption of calcium of 30% from mixed diets. In the USA the traditional RDA was 800 mg daily for adults aged over 25 years; this figure was based on an absorption rate of 40%. Under the new dietary reference intakes, adequate intakes (AI) for calcium have been set, which are higher in some age groups than the previous RDAs.[3] For adults aged up to 50 years the AI is 1 g daily, and for those 51 years or older, it is 1.2 g daily.[3] The tolerable upper intake is considered to be 2.5 g daily.[3]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Subcommittee on the tenth edition of the RDAs, Food and Nutrition Board, Commission on Life Sciences, National Research Council. *Recommended dietary allowances*. 10th ed. Washington, DC: National Academy Press, 1989. Also available at: http://www.nap.edu/openbook.php?isbn=0309046335 (accessed 21/07/08)
3. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309065507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Calcimax; Calcio Cit Simple†; Calcional Citrato; Calcium-Sandoz; Citramar†; Findeclin Combi; Ostram; Procalcio†; Raffo-Ca; Regucal; Renacalcio; Royen; Sigmacal; *Austral.*: Celloids CP 57†; Citracal; Sandocal†; *Austria*: Calcium Fresenius; Calcium-Sandoz†; Calcium-Sandoz; OsvaRen; Phos-Ex; *Belg.*: Calcicio; PhosLo; Sandoz Calcium; Sandoz Calcium; *Braz.*: Calcium-Sandoz F; Calcium-Sandoz; Miocalven; *Canad.*: Calcifortet; Calciject; Calcium-Sandoz; Citracal + D; Dicalcine†; Formula Cal-Phos†; Osteocit; PhosLo; Solucal; *Chile*: Calcimax; Calcimin†; Calcium-Sandoz†; Kaplus; Ostram†; PhosLo; *China*: A Si Ka (阿斯卡); Gai Tian Li (盖天力); Hong Tai (乳泰); Huoligai (活力钙); Jia Jia Gai (佳加盖); Kai Ti (凯替); Si Lin Tuo (斯林妥); Si Te Li (司特立); Wei Li Tian (维立添); You Ni Le (尤尼乐); *Cz.*: Calcium Biotika; Phosphosorb; *Denm.*: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex; *Fin.*: Calcium-Sandoz†; Calcium-Sandoz; Phos-Ex; Selutrio; *Fr.*: CAL'Ocean†; Calcium-Sandoz; Glucalcium†; Ostram; Phosphosorb; *Ger.*: Calcet; Calciretard; Calcitrat; Calcium-Sandoz†; Cerasorb; OsvaRen; Phos-Ex†; Phosphosorb; *Gr.*: Calciforte; Decalcit; Neocalcit; Ormitac; Osteorel; Osteus; Ostram; Phosphosorb; *Hong Kong*: Calcium Unison; Calcium-Sandoz; Calforte†; Citracal†; Citracium; Kalac†; Mega-Cal; *Hung.*: Bano; Calcimusc; Calcium-Sandoz; Citrokalcium; *India*: Calbin; Calzorb; CCM; Ezorb; Hypophos; Milkal-G; Miltab; Phosforid; *Indon.*: Calnic; Dumocalcin; Lakalsik; Licokalk; Pro Kalk; *Irl.*: Calcium-Sandoz; Everose†; Phosex; Sandocal; *Israel*: Calcium-Sandoz†; Calcium-Sandoz Ferrocal; *Ital.*: Calcetat; Calcium-Sandoz; *Malaysia*: Calcium Upha†; *Mex.*: Bionokaltran; Calcidef; Calcifox†; Calcigenol Doble; Calciofem; Calcium-Sandoz; Calcival; *Neth.*: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex†; PhosLo; Phosphosorb; *Norw.*: Calcium-Sandoz; Phos-Ex; *NZ*: Calcium-Sandoz†; *Philipp.*: Calcebone; Calcinate; United Home Calactate; *Pol.*: Calcium Calfit†; Calcium Syrop; Calcium-Sandoz Forte; Ostical†; Ostram; Sanosvit Calcium; Satural; *Port.*: Calcium-Sandoz; Extraneal; Phosphosorb; Sandocal†; *Rus.*: Calcium-Sandoz Forte (Кальций-Сандоз Форте); Vita-Iodurol (Вита-йодурол); *S.Afr.*: Calcium-Sandoz; Glucal†; *Singapore*: Calcium-Sandoz Forte; Citracal†; Dorama-neo; Hydrofluoric Acid Antidote; Os-Cal; Vitacal; *Spain*: Calcio 20 Emulsion; Calcium-Sandoz Forte†; Ibercal; Ostram; PhosLo; Royen; Suplecal; Tepox Cal; *Swed.*: Calcium-Sandoz; Calcium-Sandoz; Phos-Ex; *Switz.*: AcetaPhos; Calcium-Sandoz; Calcium-Sandoz; Renacet; *Thai.*: BO Cal; Cal-Cit; Cal-med; Calcetate; Calcion; Calcipac; Calcium Unison†; Calcium Utopian; Calcium-Sandoz; Calsorp; Caltab Forte†; Calvin; Cebrin-Fe; Kal-Forte; Lo-P-Caps; *Turk.*: Anti-Posfat Ca; Calcium-Sandoz; Calcium-Sandoz; Phos-Bind; Phos-Ex; Phos-Out; *UK*: BioCalth; Calcium-Sandoz; Caphosol; Ostram; Phos-Ex; PhosLo; Sandocal; *USA*: Cal-C; Cal-Citrate; Cal-G; Cal-Lac; Calphron; Caphosol; Citracal; Eliphos; Oyster Calcium; PhosLo; Posture; Prelief; *Venez.*: Calcibon; Calcitrex; Calcium-Sandoz; Calcium-Sandoz; Citracal; Maxical; Oscale.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Used as an adjunct in:. *Hung.*: Kalmopyrin; *Pol.*: Polopiryna C Plus; *Swed.*: Deltison.

Homoeopathic Preparations. *Austria*: China Med Complex; Colchicum Med Complex; Globuli gegen Gelenkschmerzen; Lymphomyosot; Osanit Zahnungskugelchen: Osteoplex; Steiroplex; Zahnkugelchen; *Canad.*: Biochemic Phosphates; Calms Forte 4 Kids; Calms Forte; Combinaison†; Diamite; Fibromyalgie; Fucus L111†; Hylands Bioplasma; Hylands Formula CF; Hylands Formula NT; Hylands Kinder-T†; Ikoplex 5†; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Osteel†; Phyto-Cal; Rexorubia†; Sorinoheel; Teething; Ton 1 Complex†; Ursical Formula†; Urticalcin; *Chile*: Bioactiv D; Ikoplex No 15; Ikoplex No 1; Ikoplex No 20; Ikoplex No 22; Ikoplex No 2; Ikoplex No 4; Ikoplex No 6; Ikoplex No 9; *Cz.*: Lymphomyosot; *Fr.*: Abbe Chaupitre no 1†; Abbe Chaupitre no 6; Abbe Chaupitre no 91†; Calcarea Compose; Dolisedal†; Fucus Complexe No 111; Hypophysis Complexe No 31†; L 28; Osteocynesine; Rexorubia; Triphosphates; *Ger.*: Alho-Arthrosan N; Araniforce rheuma†; Disci Bamb; Disco-cyl Ho-Len-Complex; Drufusan N†; Drufusan; Girheulit HM†; Infi-Symphytum; Lumbago-Gastreu S R11; Lymphomyosot N; Lymphomyosot; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Osanit; Osteoplex; Pascoe-Agil HOM; Ranocalcin HM; Refesan T; Roth's RKT Tropfen; Steirocall; Steiroplex†; *Hung.*: Lymphomyosot; Osteoheel; *Neth.*: Dulcarhus-Gastreu R11; Emvita 2; Kind 0-6 Caltrivat; Lymfelite; Osteocynesine†; *Port.*: Osteocynesine; *S.Afr.*: Lymphomyosot; *Switz.*: Osteoheel; Regenaplex Nr 38b; Silacten; Urticalcin; *UK*: New Era Elasto; New Era Nervone; *Ukr.*: Immunokind (Иммунокинд); Lymphomyosot (Лимфомиозот); Lymphomyosot N (Лимфомиозот Н).

Pharmacopoeial Preparations

BP 2014: Calcium and Ergocalciferol Tablets; Calcium Chloride Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Chewable Calcium and Ergocalciferol Tablets; Chewable Calcium Gluconate Tablets; Compound Sodium Lactate Infusion; Effervescent Calcium Gluconate Tablets;

BPC 1973: Calcium with Vitamin D Tablets;

USP 36: Aluminum Sulfate and Calcium Acetate for Topical Solution; Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution; Calcium Acetate Tablets; Calcium and Vitamin D with Minerals Tablets; Calcium Chloride Injection; Calcium Citrate Tablets; Calcium Glubionate Syrup; Calcium Gluceptate Injection; Calcium Gluconate Injection; Calcium Gluconate Tablets; Calcium Lactate Tablets; Calcium Levulinate Injection; Calcium with Vitamin D Tablets; Dibasic Calcium Phosphate Tablets; Half-strength Lactated Ringer's and Dextrose Injection; Lactated Ringer's and Dextrose Injection; Lactated Ringer's Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Tablets; Potassium Chloride in Lactated Ringer's and Dextrose Injection; Ringer's and Dextrose Injection; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Magnesium

Magnesio; Magnésium; Magnez; Магний.

Mg=24.305

UNII — I38ZP9992A (magnesium); T6V3LHY838 (magnesium ion).

Description. Magnesium is a cation given as various magnesium-containing salts.

Incompatibility. Magnesium salts have been reported to be incompatible with a wide range of drugs.

Magnesium Acetate

Acetato magnésico; Magnesii Acetas Tetrahydricus; Magnesio, acetato de; Magnésium (acétate de) tétrahydraté; Magnesiumacetattetrahydrat; Magnesiumasetaattitetrahydraatti; Magnézium acetáttetrahidrát; Magnezu octan; Magnio acetatas tetrahidratas; Octan hořečnatý tetrahydrát; Ацетат Магния; Уксуснокислый Магний.

$C_4H_6MgO_4.4H_2O$=214.5.

CAS — 142-72-3 (anhydrous magnesium acetate); 16674-78-5 (magnesium acetate tetrahydrate).

UNII — 0E95JZY48K (magnesium acetate); I01G0EJC38 (magnesium acetate tetrahydrate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Acetate Tetrahydrate). Colourless crystals or a white or almost white, crystalline powder. Freely soluble in water and in alcohol. A 5% solution in water has a pH of 7.5 to 8.5.

Equivalence. Each g of magnesium acetate (tetrahydrate) represents about 4.7 mmol of magnesium and the equivalent of bicarbonate. Magnesium acetate (tetrahydrate) 8.83 g is equivalent to about 1 g of magnesium.

Magnesium Ascorbate

Ascorbato magnésico; Magnesio, ascorbato de; Магния Аскорбат.

$(C_6H_7O_6)_2Mg$=374.5.

CAS — 15431-40-0.

UNII — 0N1G678593.

Equivalence. Each g of magnesium ascorbate (anhydrous) represents about 2.7 mmol of magnesium. Magnesium ascorbate (anhydrous) 15.4 g is equivalent to about 1 g of magnesium.

Magnesium Aspartate

Aspartato magnésico; Bázisos magnézium-aszpartát-dihidrát; Magnesii aspartas dihydricus; Magnesii hydrogenoaspartas Dihydricus; Magnesio, aspartato de; Magnésium (aspartate de) dihydraté; Magnesium Aspartate Dihydrate; Magnesiumaspartaattidihydraatti; Magnesiumaspartat-Dihydrat; Magnesiumaspartatdihydrat; Magnesium-hydrogenaspartát dihydrát; Magnio aspartatas dihidratas; Магния аспарагинат.

Magnesium aminosuccinate dihydrate; Magnesium di[(*S*)-2-aminohydrogenobutane-1,4-dioate].

$C_8H_{12}MgN_2O_8.2H_2O$=324.5.

CAS — 18962-61-3 (anhydrous magnesium aspartate); 2068-80-6 (anhydrous magnesium aspartate or magnesium aspartate dihydrate); 7018-07-7 (magnesium aspartate tetrahydrate).

ATC — A12CC05.

ATC Vet — QA12CC05.

UNII — R17X820ROL.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate form of the (*S*)-aspartate. *Ger.* includes the tetrahydrate form of the racemic aspartate.

Ph. Eur. 8: (Magnesium Aspartate Dihydrate; Magnesium Aspartate BP 2014). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water. A 2.5% solution in water has a pH of 6.0 to 8.0.

Equivalence. Each g of magnesium aspartate (dihydrate) represents about 3.1 mmol of magnesium. Magnesium aspartate (dihydrate) 13.4 g is equivalent to about 1 g of magnesium.

Each g of magnesium aspartate (tetrahydrate) represents about 2.8 mmol of magnesium. Magnesium aspartate (tetrahydrate) 14.8 g is equivalent to about 1 g of magnesium.

Magnesium Chloride

Magnesiumklorid; Chlorid hořečnatý; Chlorure de Magnésium Cristallisé; Cloreto de Magnésio; Cloruro magnésico; E511; Magnesii chloridum; Magnesio, cloruro de; Magnesium Chloratum; Magnésium, chlorure de; Magnesiumklorid; Magnézium-klorid; Magnezu chlorek; Magnio chloridas; Магния Хлорид.

$MgCl_2.xH_2O$=95.20 (anhydrous); 203.3 (hexahydrate).

CAS — 7786-30-3 (anhydrous magnesium chloride); 7791-18-6 (magnesium chloride hexahydrate).

ATC — A12CC01; B05XA11.

ATC Vet — QA12CC01; QB05XA11.

UNII — 02F3473H9O (magnesium chloride); 59XN63C8VM (anhydrous magnesium chloride).

Pharmacopoeias. *Eur.* (see p. vii), *US*, and *Viet.* include the hexahydrate.

Eur. also includes magnesium chloride 4.5-hydrate.

Ph. Eur. 8: (Magnesium Chloride Hexahydrate; Magnesii Chloridum Hexahydricum). Colourless, hygroscopic crystals. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

Ph. Eur. 8: (Magnesium Chloride 4.5-Hydrate; Magnesii Chloridum 4.5-Hydricum; Partially Hydrated Magnesium Chloride BP 2014). A white or almost white, hygroscopic, granular powder. Very soluble in water; freely soluble in alcohol. Store in airtight containers.

USP 36: (Magnesium Chloride). Colourless, odourless, deliquescent flakes or crystals, which lose water when heated to 100 degrees and lose hydrochloric acid when heated to 110 degrees. Very soluble in water; freely soluble in alcohol. pH of a 5% solution in water is between 4.5 and 7.0. Store in airtight containers.

Equivalence. Each g of magnesium chloride (hexahydrate) represents about 4.9 mmol of magnesium and 9.8 mmol of chloride. Magnesium chloride (hexahydrate) 8.36 g is equivalent to about 1 g of magnesium.

Magnesium Gluceptate

Gluceptato magnésico; Magnesio, glucoheptonato de; Magnesium Glucoheptonate; Магния Глюцептат.

$C_{14}H_{26}MgO_{16}$=474.7.

UNII — NR47LC4280.

Equivalence. Each g of magnesium gluceptate (anhydrous) represents about 2.1 mmol of magnesium. Magnesium gluceptate (anhydrous) 19.5 g is equivalent to about 1 g of magnesium.

Magnesium Gluconate

Gluconato magnésico; Magnesii gluconas; Magnesio, glucónato de; Magnésium, gluconate de; Magnesiumgluconat; Магния глюконат.

Magnesium D-gluconate hydrate.

$C_{12}H_{22}MgO_{14}.xH_2O$=414.6 (anhydrous)

CAS — 3632-91-5 (anhydrous magnesium gluconate); 59625-89-7 (magnesium gluconate dihydrate).

ATC — A12CC03.

ATC Vet — QA12CC03.

UNII — T42NAD2KHC.

Pharmacopoeias. In *Eur.* (see p. vii), which allows either anhydrous or hydrated forms, and in *US*, which allows either anhydrous or the dihydrate.

Ph. Eur. 8: (Magnesium Gluconate). A white or almost white, amorphous, hygroscopic, crystalline or granular powder. Freely soluble in water; slightly soluble in alcohol; very slightly soluble in dichloromethane. Store in airtight containers.

USP 36: (Magnesium Gluconate). Colourless crystals or a white powder or granules. Is odourless. Freely soluble in water; very slightly soluble in alcohol; insoluble in ether. pH of a 5% solution in water is between 6.0 and 7.8.

Equivalence. Each g of magnesium gluconate (anhydrous) represents about 2.4 mmol of magnesium. Magnesium gluconate (anhydrous) 17.1 g is equivalent to about 1 g of magnesium.

Magnesium Glycerophosphate

Glicerofosfato magnésico; Glycerofosforečnan hořečnatý; Magnesii Glycerophosphas; Magnesio, glicerofosfato de; Magnesium Glycerinophosphate; Magnésium, glycérophosphate de; Magnesiumglycerofosfat; Magnesiumglycerophosphat; Magnesiumglyserofosfaatti; Magnézium-glicerofoszfát; Magnio glicerofosfatas; Магния глицерофосфат.

$C_3H_7MgO_6P.xH_2O$=194.4 (anhydrous).

CAS — 927-20-8 (anhydrous magnesium glycerophosphate).

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Glycerophosphate). A mixture, in variable proportions, of magnesium (*R,S*)-2,3-dihydroxypropyl phosphate and magnesium 2-hydroxy-1-(hydroxymethyl)ethyl phosphate. It may be hydrated. A white or almost white, hygroscopic powder. Practically insoluble in alcohol; dissolves in dilute solutions of acids. Store in airtight containers.

Equivalence. Each g of magnesium glycerophosphate (anhydrous) represents about 5.1 mmol of magnesium. Magnesium glycerophosphate (anhydrous) 8 g is equivalent to about 1 g of magnesium.

Magnesium Lactate

Lactato magnésico; Magnesii Lactas; Magnesio, lactato de; Magnésium, lactate de; Magnesiumlaktaatti; Magnesiumlaktat; Magnesium-laktát; Magnezu mleczan; Молочнокислый Магний; Магния Лактат.

Magnesium 2-hydroxypropionate.

$C_6H_{10}MgO_6$=202.4.

CAS — 18917-93-6.

ATC — A12CC06.

ATC Vet — QA12CC06.

UNII — MT6QI8324A.

Pharmacopoeias. *Eur.* (see p. vii) includes the dihydrate.

Ph. Eur. 8: (Magnesium Lactate Dihydrate; Magnesii Lactas Dihydricus). A white or almost white, crystalline or granular powder. Slightly soluble in water; soluble in boiling water; practically insoluble in alcohol. A 5% solution in water has a pH of 6.5 to 8.5.

Equivalence. Each g of magnesium lactate (anhydrous) represents about 4.9 mmol of magnesium. Magnesium lactate (anhydrous) 8.33 g is equivalent to about 1 g of magnesium.

Magnesium Phosphate

Fosfato magnésico trifásico; Magnesio, fosfato de; Tribasic Magnesium Phosphate; Trimagnesium Phosphate; Опрофосфат Магния Трехзамещенный.

$Mg_3(PO_4)_2.5H_2O$=352.9.

CAS — 7757-87-1 (anhydrous magnesium phosphate); 10233-87-1 (magnesium phosphate pentahydrate).

ATC — B05XA10.

ATC Vet — QB05XA10.

UNII — 453COF7817 (magnesium phosphate pentahydrate); XMK14ETW2D (anhydrous magnesium phosphate).

Pharmacopoeias. In *US*.

Ger. includes Magnesium Hydrogen Phosphate Trihydrate ($MgHPO_4.3H_2O$ = 174.3).

USP 36: (Magnesium Phosphate). A white, odourless, powder. Almost insoluble in water; readily soluble in dilute mineral acids.

Equivalence. Each g of magnesium phosphate (pentahydrate) represents about 8.5 mmol of magnesium and 5.7 mmol of phosphate. Magnesium phosphate (pentahydrate) 4.84 g is equivalent to about 1 g of magnesium.

Magnesium Pidolate *(pINNM)*

Magnesii Pidolas; Magnesio, pidolato de; Magnésium, pidolate de; Magnesium Pyroglutamate; Magnesiumpidolaatti; Magneslumpidolat; Magnesium-pidolát; Magnézium-pidolát; Magnio pidolatas; Pidolate de Magnesium; Pidolato de magnesio; Pidolato magnésico; Магния Пидолат.

Magnesium 5-oxopyrrolidine-2-carboxylate.

$(C_5H_6NO_3)_2Mg$=280.5.

CAS — 62003-27-4.

ATC — A12CC08.

ATC Vet — QA12CC08.

UNII — V5PC588N7G.

Pharmacopoeias. In *Eur.* (see p. vii).

Ph. Eur. 8: (Magnesium Pidolate). An amorphous, white or almost white, hygroscopic powder. Very soluble in water; practically insoluble in dichloromethane; soluble in methyl alcohol. A 10% solution in water has a pH of 5.5 to 7.0. Store in airtight containers.

Equivalence. Each g of magnesium pidolate (anhydrous) represents about 3.6 mmol of magnesium. Magnesium pidolate (anhydrous) 11.5 g is equivalent to about 1 g of magnesium.

Magnesium Sulfate

518; Epsom Salts; Magnesii Sulfas; Magnesio, sulfato de; Magnésium, sulfate de; Magnesium Sulphate; Magnesiumsulfaatti; Magnesiumsulfat; Magnézium-szulfát; Magnezu siarczan; Magnio sulfatas; Sal Amarum; Sel Anglais; Sel de Sedlitz; Síran hořečnatý; Sulfato magnésico; Сульфат Магния.

$MgSO_4.xH_2O$=120.4 (anhydrous); 246.5 (heptahydrate).

CAS — 7487-88-9 (anhydrous magnesium sulfate); 10034-99-8 (magnesium sulfate heptahydrate).

ATC — A06AD04; A12CC02; B05XA05; D11AX05; V04CC02.

ATC Vet — QA06AD04; QA12CC02; QB05XA05; QD11AX05; QV04CC02.

UNII — 4L30MJ2U7L (anhydrous magnesium sulfate); DE08037SAB (magnesium sulfate); E2L2TK027P (magnesium sulfate monohydrate); SK47B8698T (magnesium sulfate heptahydrate).

Pharmacopoeias. *Chin.*, *Eur.* (see p. vii), *Int.*, *Jpn*, and *Viet.* include the heptahydrate.

US allows the dried form, the monohydrate, or the heptahydrate form.

The dried form is included in *Br.*

Ph. Eur. 8: (Magnesium Sulfate Heptahydrate; Magnesii Sulfas Heptahydricus). A white or almost white, crystalline powder or brilliant, colourless crystals. Freely soluble in water; very soluble in boiling water; practically insoluble in alcohol.

The BP 2014 gives Epsom Salts as an approved synonym.

BP 2014: (Dried Magnesium Sulfate). A white odourless or almost odourless powder, prepared by drying magnesium sulfate (heptahydrate) at 100 degrees until it has lost about 25% of its weight; it contains 62 to 70% of $MgSO_4$. Freely soluble in water; more rapidly soluble in hot water.

The BP gives Dried Epsom Salts as an approved synonym.

USP 36: (Magnesium Sulfate). It is the dried form, monohydrate, or the heptahydrate. Small, colourless crystals, usually needle-like. It effloresces in warm dry air. Soluble 1 in 0.8 of water and 1 in 0.5 of boiling water; freely but slowly soluble 1 in 1 of glycerol; sparingly soluble in alcohol. pH of a 5% solution in water is between 5.0 and 9.2.

Equivalence. Each g of magnesium sulfate (heptahydrate) represents about 4.1 mmol of magnesium. Magnesium sulfate (heptahydrate) 10.1 g is equivalent to about 1 g of magnesium.

Uses and Administration

Some magnesium salts are given as a source of magnesium ions in the treatment of **magnesium deficiency and hypomagnesaemia** (p. 1776.3). Doses may be expressed in terms of mmol or mEq of magnesium, mass (mg) of magnesium, or mass of magnesium salt (for comparative purposes, see Table 2, below). In acute or severe hypomagnesaemia, magnesium may be given parenterally, usually as the chloride or sulfate. One suggested regimen is 20 mmol of magnesium in 1 litre of infusion solution (glucose 5% or sodium chloride 0.9%) given *intravenously* over 3 hours. Alternatively, 35 to 50 mmol of magnesium in 1 litre of infusion solution may be given over a period of 12 to 24 hours. Up to a total of 160 mmol may be required over 5 days. In those receiving parenteral nutrition, doses of about 12 mmol magnesium daily may be given to prevent recurrence of the deficit. Magnesium sulfate can also be given *intramuscularly* for severe magnesium deficiency. A recommended dose is 1 mmol/kg of magnesium, given over a period of 4 hours; this route is stated to be painful. Careful monitoring of plasma-magnesium and other electrolyte concentrations is essential. Doses should be reduced in renal impairment. Other salts which are, or have been, used parenterally include magnesium ascorbate, magnesium aspartate hydrochloride, and magnesium pidolate.

In simple deficiency states magnesium salts may be given *orally* in doses adjusted according to individual requirements. For preventing recurrence of hypomagnesaemia, doses of 24 mmol daily in divided doses have been recommended. Salts that are, or have been, used orally include magnesium aspartate, magnesium chloride, magnesium citrate, magnesium fluoride, magnesium gluceptate, magnesium gluconate, magnesium glycerophosphate, magnesium lactate, magnesium levulinate, magnesium orotate, and magnesium pidolate.

Magnesium salts such as the carbonate, hydroxide, oxide, and trisilicate are widely used for their **antacid** properties (p. 1803.1). Magnesium salts also act as **osmotic laxatives** (p. 1804.1); the salts generally used for this purpose are magnesium sulfate (an oral dose of 5 to 10 g in 250 mL of water being given for rapid bowel evacuation) and magnesium hydroxide (p. 1857.2).

Table 2. Some magnesium salts and their magnesium content.

Magnesium salt	Magnesium content per g		
	mg	mmol	mEq
Magnesium acetate (tetrahydrate)	113	4.7	9.3
Magnesium ascorbate (anhydrous)	65	2.7	5.3
Magnesium aspartate (dihydrate)	75	3.1	6.2
Magnesium aspartate (tetrahydrate)	67	2.8	5.5
Magnesium chloride (hexahydrate)	120	4.9	9.8
Magnesium gluceptate (anhydrous)	51	2.1	4.2
Magnesium gluconate (anhydrous)	59	2.4	4.8
Magnesium glycerophosphate (anhydrous)	125	5.1	10.3
Magnesium lactate (anhydrous)	120	4.9	9.9
Magnesium phosphate (pentahydrate)	207	8.5	17.0
Magnesium pidolate (anhydrous)	87	3.6	7.1
Magnesium sulfate (heptahydrate)	99	4.1	8.1

Parenteral magnesium sulfate has some specific uses. It is used for the emergency treatment of some **arrhythmias** such as torsade de pointes (see below) and those associated with hypokalaemia (p. 1777.2). The usual dose is 2 g of magnesium sulfate (8 mmol of magnesium) given intravenously over 10 to 15 minutes and repeated once if necessary.

Parenteral magnesium sulfate is also used for the treatment and prevention of seizures in pregnant women with **eclampsia and pre-eclampsia** (see below). Debate continues as to which dosage regimen is most appropriate. Typically an intravenous loading dose of 4 g of magnesium sulfate (16 mmol of magnesium) is given over 5 to 15 minutes. This is then followed by either an infusion of 1 g (4 mmol magnesium) per hour (for at least 24 hours after the last seizure) or by deep intramuscular injection of 5 g (20 mmol magnesium) into each buttock then 5 g intramuscularly every 4 hours (for at least 24 hours after the last seizure). Should seizures recur under either regimen, then an additional intravenous dose of 2 to 4 g can be given. It is essential to monitor for signs of hypermagnesaemia, and to stop magnesium dosage should this occur. Doses should be reduced in renal impairment.

The use of magnesium sulfate in **acute myocardial infarction** and **premature labour** is discussed below (see below and p. 1789.1, respectively).

Dried magnesium sulfate has been used in the form of Magnesium Sulphate Paste (BP 2014) as an application to inflammatory skin conditions such as boils and carbuncles, but prolonged or repeated use may damage the surrounding skin.

General references.

1. McLean RM. Magnesium and its therapeutic uses: a review. *Am J Med* 1994; 96: 63–76.
2. Fawcett WJ, *et al.* Magnesium: physiology and pharmacology. *Br J Anaesth* 1999; 83: 302–20.
3. Fox C, *et al.* Magnesium: its proven and potential clinical significance. *South Med J* 2001; 94: 1195–1201.
4. Gums JG. Magnesium in cardiovascular and other disorders. *Am J Health-Syst Pharm* 2004; 61: 1569–76.

Anaesthesia. Magnesium sulfate has been used to prevent the undesirable haemodynamic response sometimes associated with intubation (p. 2028.1). It has also been tried in the treatment of postoperative shivering (p. 1897.2).

Arrhythmias. Cardiac function is strongly influenced by electrolyte concentrations and some cardiac arrhythmias (p. 1266.1) may be associated with magnesium deficiency. Parenteral magnesium has a role in the management of torsade de pointes and some other arrhythmias, and has also been used to prevent postoperative atrial fibrillation. However, for a review of the debate over magnesium's possible antiarrhythmic effect in patients with myocardial infarction, see Myocardial Infarction, below.

Further references.

1. Frick M, *et al.* The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patients with persistent atrial fibrillation. *Eur Heart J* 2000; 21: 1177–85.
2. Stuhlinger HG, *et al.* Der Stellenwert von Magnesium bei Herzrhythmusstorungen. *Wien Med Wochenschr* 2000; 150: 330–4.
3. Piotrowski AA, Kalus JS. Magnesium for the treatment and prevention of atrial tachyarrhythmias. *Pharmacotherapy* 2004; 24: 879–95.
4. Shiga T, *et al.* Magnesium prophylaxis for arrhythmias after cardiac surgery: a meta-analysis of randomized controlled trials. *Am J Med* 2004; 117: 325–33.
5. Aighamdi AA, *et al.* Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis. *J Card Surg* 2005; 20: 293–9.
6. Miller S, *et al.* Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis. *Heart* 2005; 91: 618–23.
7. Ho KM, *et al.* Use of intravenous magnesium to treat acute onset atrial fibrillation: a meta-analysis. *Heart* 2007; 93: 1433–40.
8. Onalan O, *et al.* Meta-analysis of magnesium therapy for the acute management of rapid atrial fibrillation. *Am J Cardiol* 2007; 99: 1726–32.

Eclampsia and pre-eclampsia. Parenteral magnesium sulfate has become the preferred treatment for seizures associated with **eclampsia** (p. 511.1). Studies and systematic reviews have shown it to be more effective than phenytoin,[1,2] diazepam,[1,3] or lytic cocktail,[4] as well as causing fewer adverse effects. Its advantages included a rapid effect and lack of sedation in the mother or the infant.[5] It was also considered to have a wide safety margin with the added security of calcium gluconate being an easily available antidote should overdose occur. Subsequent meta-analysis[6] and systematic review[2-4] reinforced this favourable view.

Magnesium sulfate may also be used to prevent eclampsia in **pre-eclamptic** patients; studies have shown it to be more effective than phenytoin,[7] or nimodipine.[8] A randomised placebo-controlled study[9] involving over 10 000 women in 33 countries found that treatment with magnesium sulfate approximately halved the risk of developing eclampsia; the number of maternal deaths was also less in the treatment group although the differences in risk between this group and the placebo group were not significant.

Despite some concerns about the effects on the fetus of magnesium sulfate use in premature labour, (see p. 1789.1), many,[10,11] including WHO, consider magnesium sulfate the drug of choice for both treatment and prevention of eclampsia. Moreover, follow-up studies of the international study mentioned above found that it was not associated with an increased risk of death or disability in the children at 18 months[12] and in the mothers at 2 years.[13]

1. The Eclampsia Trial Collaborative Group. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; 345: 1455–63. Correction. *Ibid.*; 346: 258.
2. Duley L, Henderson-Smart DJ. Magnesium sulphate versus phenytoin for eclampsia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 09/03/09).
3. Duley L, Henderson-Smart DJ. Magnesium sulphate versus diazepam for eclampsia. Available in The Cochrane Database of Systematic Reviews: Issue 4. Chichester: John Wiley; 2003 (accessed 09/03/09).
4. Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. Available in The Cochrane Database of Systematic Reviews: Issue 3. Chichester: John Wiley; 2000 (accessed 09/03/09).
5. Saunders N, Hammersley B. Magnesium for eclampsia. *Lancet* 1995; 346: 788–9.
6. Chien PFW, *et al.* Magnesium sulphate in the treatment of eclampsia and pre-eclampsia: an overview of the evidence from randomised trials. *Br J Obstet Gynaecol* 1996; 103: 1085–91.
7. Lucas MJ, *et al.* A comparison of magnesium sulfate with phenytoin for the prevention of eclampsia. *N Engl J Med* 1995; 333: 201–5.
8. Belfort MA, *et al.* A comparison of magnesium sulfate and nimodipine for the prevention of eclampsia. *N Engl J Med* 2003; 348: 304–11.
9. The Magpie Trial Collaborative Group. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; 359: 1877–90.
10. Roberts JM, *et al.* Preventing and treating eclamptic seizures. *BMJ* 2002; 325: 609–10.
11. WHO. *Managing complications in pregnancy and childbirth: a guide for midwives and doctors.* GENEVA: WHO, 2000. Available at: http://whqlibdoc.who.int/publications/2007/9241545879_eng.pdf (accessed 20/08/10)
12. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for children at 18 months. *BJOG* 2007; 114: 289–99.
13. Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia—outcome for women at 2 years. *BJOG* 2007; 114: 300–9.

Hypokalaemia. Potassium and magnesium homoeostasis are linked, and hypokalaemia with increased urine potassium excretion may occur in patients with hypomagnesaemia. In this situation, correction of potassium deficit usually requires magnesium to be given as well. Magnesium sulfate at doses greater than those required to correct hypomagnesaemia has been associated with greater improvements in potassium balance than doses just sufficient to correct hypomagnesaemia.[1]

1. Hamill-Ruth RJ, McGory R. Magnesium repletion and its effect on potassium homeostasis in critically ill adults: results of a double-blind, randomized, controlled trial. *Crit Care Med* 1996; 24: 38–45.

Migraine. Low magnesium concentrations are thought to be important in the pathogenesis of migraine (p. 670.3), but the precise role of magnesium supplementation in the disorder remains to be determined.[1] In a double-blind study,[2] 24 mmol magnesium daily (in the form of oral magnesium citrate) reduced the incidence of migraine headache by 42% compared with a reduction of 16% with placebo. However, in another similar study,[3] 20 mmol magnesium daily (in the form of oral magnesium aspartate hydrochloride) was no more effective than placebo in producing a 50% reduction in migraine frequency or intensity. Intravenous magnesium sulfate has shown benefit in the treatment of migraine attacks,[4] especially in those with aura,[5,6] or in patients with low serum-magnesium levels.[7]

1. Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. *Clin Neurosci* 1998; 5: 24–7.
2. Peikert A, *et al.* Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-blind randomized study. *Cephalalgia* 1996; 16: 257–63.
3. Pfaffenrath V, *et al.* Magnesium in the prophylaxis of migraine: a double-blind placebo-controlled study. *Cephalalgia* 1996; 16: 436–40.
4. Demirkaya Ş, *et al.* Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. *Headache* 2001; 41: 171–7.
5. Bigal ME, *et al.* Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura: a randomized, double-blind, placebo-controlled study. *Cephalalgia* 2002; 22: 345–53.
6. Bigal ME, *et al.* Eficácia de três drogas sobre a aura migranosa: um estudo randomizado placebo controlado. *Arq Neuropsiquiatr* 2002; 60: 406–9.
7. Mauskop A, *et al.* Intravenous magnesium sulphate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study. *Clin Sci* 1995; 89: 633–6.

Myocardial infarction. Magnesium has an important physiological role in maintaining the ion balance in muscle including the myocardium. Magnesium might have an antiarrhythmic effect (see also Arrhythmias, above) and protect the myocardium against reperfusion injury including myocardial stunning (delayed recovery of myocardial contractility function). Intravenous magnesium salts have been used for cardiac arrhythmias and in an overview of studies in patients with suspected myocardial infarction their use, generally within 12 hours of the onset of chest pain, reduced mortality.[1] The beneficial effect on mortality appeared to be confirmed by the LIMIT-2 study[2] in which 8 mmol of magnesium was given by intravenous injection before thrombolysis and followed

by a maintenance infusion of 65 mmol over the next 24 hours. Benefit was confirmed at follow-up an average of 2.7 years later;[3] however, there was no evidence of an antiarrhythmic effect. These beneficial effects were not borne out by the larger ISIS-4 study,[4] although there were slight differences in the magnesium regimen and its timing which might have played a part in these contradictory results. In an attempt to resolve the controversy, the MAGIC trial[5] was designed to test the hypothesis that early use of magnesium in a similar dose to that used in the LIMIT-2 study would reduce short-term mortality in patients with ST elevation myocardial infarction. No benefit or harm of magnesium was observed. A later systematic review of intravenous magnesium for acute myocardial infarction[6] concluded that although it may have some beneficial effects, such as reducing certain arrhythmias, magnesium is unlikely to reduce mortality and may increase certain adverse effects. At present the routine use of magnesium in myocardial infarction (p. 1257.1) cannot be recommended.

Patients with acute myocardial infarction may have magnesium deficiency and long-term treatment with oral magnesium has been tried, but in one study was associated with an increased risk of adverse cardiac events and could not be recommended for secondary prevention.[7]

1. Teo KK, *et al.* Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991; 303: 1499–1503.
2. Woods KL, *et al.* Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992; 339: 1553–8.
3. Woods KL, Fletcher S. Long-term outcome after intravenous magnesium sulphate in suspected acute myocardial infarction: the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1994; 343: 816–19.
4. Fourth International Study of Infarct Survival Collaborative Group. ISIS–4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345: 669–85.
5. The Magnesium in Coronaries (MAGIC) Trial Investigators. Early administration of intravenous magnesium to high-risk patients with acute myocardial infarction in the Magnesium in Coronaries (MAGIC) trial: a randomised controlled trial. *Lancet* 2002; 360: 1189–96.
6. Li J, *et al.* Intravenous magnesium for acute myocardial infarction. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2007 (accessed 09/03/09).
7. Gallae AM, *et al.* Influence of oral magnesium supplementation on cardiac events among survivors of an acute myocardial infarction. *BMJ* 1993; 307: 585–7.

Porphyria. Magnesium sulfate is one of the drugs that has been used for seizure prophylaxis in patients with porphyria who continue to experience convulsions while in remission.

Premature labour. Magnesium sulfate has been given intravenously to suppress initial uterine contractions in the management of premature labour[1-3] (p. 2131.1). Although it has been found to possess similar efficacy to beta$_2$ agonists,[4,5] and is widely used, in particular in the USA, a systematic review[6] concluded it was ineffective at delaying birth or preventing preterm birth. Other magnesium salts have also sometimes been given orally.[7,8]

Retrospective observational studies found a lower incidence of cerebral palsy in children with birth-weights of less than 1500 g when mothers were treated with magnesium sulfate for pre-eclampsia, eclampsia or premature labour.[9,10] However, increased total paediatric mortality was noted in an interim analysis of a study of antenatal magnesium sulfate in preterm labour,[11] and the study was subsequently stopped. Although they considered the safety of magnesium sulfate well established in gestation at term, the authors cautioned against the use of magnesium sulfate in very preterm labour. Subsequent studies found that magnesium sulfate was associated with increased perinatal mortality in low birth-weight offspring, particularly when doses of more than 48 g were used,[12] and that neonates with intraventricular haemorrhage (p. 1128.3) had mothers with higher serum-magnesium concentrations at delivery.[13] Some have commented[14,15] on other results, including studies of magnesium for treatment and prevention of eclampsia (see p. 1788.2), and concluded, along with a systematic review,[6] that its use as a tocolytic increased the risk of infant mortality. Nevertheless, further study has been undertaken on the use of magnesium sulfate solely for neuroprotection in preterm infants. More than 2000 women at high risk for premature delivery (gestation of 24 to 31 weeks and birth planned or expected within 2 to 24 hours), were included in a randomised, placebo-controlled study.[16] There was a significant decrease in the risk of moderate or severe cerebral palsy in the infants of women given magnesium sulfate, and the risk of paediatric death was slightly, but not significantly, increased. A similar study[17] in more than 1000 women also found significantly fewer cases of substantial motor dysfunction (including cerebral palsy) in infants who had been exposed to prenatal magnesium sulfate. In this study, however, the risk of death was slightly decreased. A systematic review[18] of 5 studies, including these two, concluded that magnesium sulfate used for neuroprotection reduced the risk of cerebral palsy, and did not increase the risk of paediatric death. However, it was still unclear which patients might benefit most, and questions remained about the most appropriate dose and timing of administration, whether maintenance therapy is needed, and whether treatment should be repeated.

Although magnesium sulfate is widely used, the American College of Obstetricians and Gynecologists does not promote it (or any drug) for first-line tocolysis.[19] It is not recommended in Europe,[20] and some in the USA have called for such use to be stopped.[21,22]

1. Amon E, *et al.* Tocolysis with advanced cervical dilatation. *Obstet Gynecol* 2000; 95: 358–62.
2. Terrone DA, *et al.* A prospective, randomized, controlled trial of high and low maintenance doses of magnesium sulfate for acute tocolysis. *Am J Obstet Gynecol* 2000; 182: 1477–82.
3. Katz VL, Farmer RM. Controversies in tocolytic therapy. *Clin Obstet Gynecol* 1999; 42: 802–19.
4. Wilkins IA, *et al.* Efficacy and side effects of magnesium sulfate and ritodrine as tocolytic agents. *Am J Obstet Gynecol* 1988; 159: 685–9.
5. Chau AC, *et al.* A prospective comparison of terbutaline and magnesium for tocolysis. *Obstet Gynecol* 1992; 80: 847–51.
6. Crowther CA, *et al.* Magnesium sulphate for preventing preterm birth in threatened preterm labour. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2002 (accessed 21/06/05).
7. Martin RW, *et al.* Comparison of oral ritodrine and magnesium gluconate for ambulatory tocolysis. *Am J Obstet Gynecol* 1988; 158: 1440–3.
8. Ridgway LE, *et al.* A prospective randomized comparison of oral terbutaline and magnesium oxide for the maintenance of tocolysis. *Am J Obstet Gynecol* 1990; 163: 879–82.
9. Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants? *Pediatrics* 1995; 95: 263–9.
10. Schendel DE, *et al.* Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. *JAMA* 1996; 276: 1805–10.
11. Mittendorf R, *et al.* Is tocolytic magnesium sulphate associated with increased total paediatric mortality? *Lancet* 1997; 350: 1517–18.
12. Sciudiero R, *et al.* Perinatal death and tocolytic magnesium sulfate. *Obstet Gynecol* 2000; 96: 178–82.
13. Mittendorf R, *et al.* Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage. *J Pediatr* 2002; 140: 540–6.
14. Mittendorf R, *et al.* If tocolytic magnesium sulfate is associated with excess total pediatric mortality, what is its impact? *Obstet Gynecol* 1998; 92: 308–11.
15. Mittendorf R, *et al.* The Magpie trial. *Lancet* 2002; 360: 1330–1.
16. Rouse DJ, *et al.* Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med* 2008; 359: 895–905.
17. Crowther CA, *et al.* Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA* 2003; 290: 2669–76.
18. Doyle LW, *et al.* Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2009 (accessed 12/03/09).
19. American College of Obstetricians and Gynecologists Committee on Practice Bulletins. Management of preterm labor (ACOG Practice Bulletin number 43, May 2003). *Obstet Gynecol* 2003; 101: 1039–47.
20. Di Renzo GC, Roura LC. European Association of Perinatal Medicine-Study Group on Preterm Birth. Guidelines for the management of spontaneous preterm labor. *J Perinat Med* 2006; 34: 359–66. Also available at: http://www.reference-global.com/doi/pdfplus/10.1515/JPM.2006.073 (accessed 02/07/08)
21. Grimes DA, Nanda K. Magnesium sulfate tocolysis: time to quit. *Obstet Gynecol* 2006; 108: 986–9.
22. Simhan HN, Caritis SN. Prevention of preterm delivery. *N Engl J Med* 2007; 357: 477–87.

Pulmonary hypertension of the newborn. Intravenous magnesium sulfate has been studied in persistent pulmonary hypertension of the newborn (p. 1278.2) but does not yet have an established role.

Respiratory disorders. Magnesium sulfate, given intravenously over 20 minutes in doses of 1.2 g to patients with acute exacerbations of chronic obstructive pulmonary disease (p. 1199.1) who had received inhaled salbutamol, appeared to have moderate efficacy.[1]

Infusion of magnesium has been reported to be of benefit in some patients with acute asthma (p. 1195.2), but results have been conflicting;[2-5] meta-analyses of these and other studies concluded that its routine use was not justified, but that it may benefit some patients with severe exacerbations.[6,7] A meta-analysis of 5 studies in children concluded that intravenous magnesium sulfate is likely to be an effective adjunct to standard therapy in the symptomatic treatment of moderate to severe acute childhood asthma.[8] Inhalation of magnesium has also been investigated, either alone or with salbutamol, and meta-analyses[9,10] have shown that it improves pulmonary function, particularly when given with a beta$_2$ agonist, with the best results seen in more severe cases. However, evidence of positive effects on clinically more important outcomes is lacking.

1. Skorodin MS, *et al.* Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med* 1995; 155: 496–500.
2. Skobeloff EM, *et al.* Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. *JAMA* 1989; 262: 1210–13.
3. Green SM, Rothrack SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med* 1992; 21: 260–5.
4. Ciarallo L, *et al.* Intravenous magnesium therapy for moderate to severe pediatric asthma: results of a randomized, placebo-controlled trial. *J Pediatr* 1996; 129: 809–14.
5. Silverman RA, *et al.* IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest* 2002; 122: 489–97.
6. Rowe BH, *et al.* Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2000 (accessed 21/06/05).
7. Alter HJ, *et al.* Intravenous magnesium as an adjuvant in acute bronchospasm: a meta-analysis. *Ann Emerg Med* 2000; 36: 191–7.
8. Cheuk DKL, *et al.* A meta-analysis on intravenous magnesium sulphate for treating acute asthma. *Arch Dis Child* 2005; 90: 74–7.
9. Blitz M, *et al.* Inhaled magnesium sulfate in the treatment of acute asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2005 (accessed 18/12/07).
10. Villeneuve EJ, Zed PJ. Nebulized magnesium sulfate in the management of acute exacerbations of asthma. *Ann Pharmacother* 2006; 40: 1118–24.

Stroke. Intravenous magnesium sulfate may have a neuroprotective effect in patients with stroke (p. 1269.2). A systematic review[1] found that, when given with nimodipine, daily magnesium treatment for up to 3 weeks reduced the risk of poor outcome in patients with subarachnoid haemorrhage. However, the results of an earlier randomised controlled study[2] in patients with ischaemic and non-ischaemic stroke showed no significant reduction in the risk of death or disability with a single, 24-hour infusion magnesium starting within 12 hours of an acute event.

1. Dorhout Mees S, *et al.* Calcium antagonists for aneurysmal subarachnoid haemorrhage. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 09/03/09).
2. Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium efficacy in Stroke trial): randomised controlled trial. *Lancet* 2004; 363: 439–45.

Tetanus. Magnesium sulfate has been found to minimise autonomic disturbance in ventilated patients and control spasms in non-ventilated patients when used in the treatment of tetanus (p. 2029.2).

References.
1. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia* 2002; 57: 811–17.
2. William S. Use of magnesium to treat tetanus. *Br J Anaesth* 2002; 88: 152–3.

Adverse Effects

Excessive parenteral doses of magnesium salts lead to the development of hypermagnesaemia, important signs of which are respiratory depression and loss of deep tendon reflexes, both due to neuromuscular blockade. Other symptoms of hypermagnesaemia may include nausea, vomiting, flushing of the skin, thirst, hypotension due to peripheral vasodilatation, drowsiness, confusion, slurred speech, double vision, muscle weakness, bradycardia, coma, and cardiac arrest.

Hypermagnesaemia is uncommon after oral magnesium salts except in the presence of renal impairment. Ingestion of magnesium salts may cause gastrointestinal irritation and watery diarrhoea.

Effects on the gastrointestinal tract. There are isolated reports of paralytic ileus in patients receiving magnesium salts.[1,2] Delayed intestinal transit has also been reported in a neonate who received an intramuscular overdose of magnesium.[3] See also Pregnancy, under Precautions, p. 1790.1.

1. Hill WC, *et al.* Maternal paralytic ileus as a complication of magnesium sulfate tocolysis. *Am J Perinatol* 1985; 2: 47–8.
2. Golzarian J, *et al.* Hypermagnesemia-induced paralytic ileus. *Dig Dis Sci* 1994; 39: 1138–42.
3. Narchi H. Neonatal hypermagnesemia: more causes and more symptoms. *Arch Pediatr Adolesc Med* 2001; 155: 1074.

Hypersensitivity. Hypersensitivity reactions characterised by urticaria were described in 2 women after receiving magnesium sulfate intravenously.[1]

1. Thorp JM, *et al.* Hypersensitivity to magnesium sulfate. *Am J Obstet Gynecol* 1989; 161: 889–90.

Treatment of Adverse Effects

The management of hypermagnesaemia is reviewed on p. 1776.2.

Hypermagnesaemia. A patient with hypermagnesaemia of a degree that is normally fatal was successfully treated using assisted ventilation, intravenous calcium chloride, and forced diuresis with mannitol infusions.[1] In another report, a 7-year-old boy given an Epsom salt (magnesium sulfate) enema for abdominal cramping, developed asystole and died, despite aggressive attempts at resuscitation. Such enemas should be avoided because of the risk of significant, unpredictable rectal absorption, leading to toxic hypermagnesaemia.[2]

1. Bohman VR, Cotton DB. Supralethal magnesemia with patient survival. *Obstet Gynecol* 1990; 76: 984–6.
2. Tofil NM, *et al.* Fatal hypermagnesaemia caused by an Epsom salt enema: a case illustration. *South Med J* 2005; 98: 253–6.

Precautions

Parenteral magnesium salts should generally be avoided in patients with heart block or severe renal impairment. They should be used with caution in less severe degrees of renal impairment and in patients with myasthenia gravis. Patients should be monitored for clinical signs of excess magnesium (see Adverse Effects, p. 1789.3), particularly when being treated for conditions not associated with hypomagnesaemia such as eclampsia. An intravenous preparation of a calcium salt should be available in case of toxicity. When used for hypomagnesaemia, serum-magnesium concentrations should be monitored.

Magnesium crosses the placenta. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided (see also Pregnancy, below).

Oral magnesium salts should be used cautiously in patients with renal impairment. Taking with food may decrease the incidence of diarrhoea. Chronic diarrhoea from long-term use may result in electrolyte imbalance.

Breast feeding. In breast milk samples from 10 pre-eclamptic women given magnesium sulfate, mean magnesium concentrations 24 hours after delivery were about 6.4 mg per 100 mL, and significantly higher than those in control subjects. However, by 48 and 72 hours after delivery, values were not significantly different. In both treated and control subjects, milk-magnesium concentrations were about twice those of maternal plasma concentrations. Although total doses of magnesium given to mothers may differ, the authors considered any increased magnesium load to a breast-fed infant to be quite small, about 1.5 mg of additional magnesium daily, and unlikely to significantly alter magnesium clearance from the neonate.[1] Based on this, the American Academy of Pediatrics considers that use of magnesium sulfate is therefore usually compatible with breast feeding.[2]

1. Cruikshank DP, *et al.* Breast milk magnesium and calcium concentrations following magnesium sulfate treatment. *Am J Obstet Gynecol* 1982; 143: 685–8.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; 108: 776–89. [Retired May 2010] Correction. *ibid.*: 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 18/05/04)

Hepatic disorders. Severe hypermagnesaemia and hypercalcaemia developed in 2 patients with hepatic encephalopathy given magnesium sulfate enemas; both patients died, one during and one after asystole. It was recommended that patients with liver disease who might develop renal impairment, or in whom renal failure is established, should not be prescribed enemas containing magnesium for treatment of hepatic encephalopathy as serious magnesium toxicity can occur, which may contribute to death.[1]

1. Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *BMJ* 1986; 293: 1013–14. Correction. *ibid.*: 1222.

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies magnesium sulfate as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Pregnancy. The meconium-plug syndrome (abdominal distention and failure to pass meconium) has been described in 2 neonates who were hypermagnesaemic after their mothers had received magnesium sulfate for eclampsia.[1] It was believed that the hypermagnesaemia may have depressed the function of intestinal smooth muscle. See also Effects on the Gastrointestinal Tract, p. 1789.3. In 36 hypermagnesaemic infants born to pre-eclamptic mothers treated with magnesium sulfate, significant neurobehavioural impairment persisted for over 24 hours after birth. Impairment was manifest by prolonged weakness in activities such as head lag, ventral suspension, suck reflex, and cry response; improvement corresponded to the decrease in plasma-magnesium concentrations.[2]

In studies in women with[3] and without[4] pre-eclampsia there were decreases in short-term fetal heart rate variability when women were given intravenous magnesium sulfate; however, although variability is considered a sign of fetal well-being the decrease was considered clinically insignificant.

1. Sokal MM, *et al.* Neonatal hypermagnesemia and the meconium-plug syndrome. *N Engl J Med* 1972; 286: 823–5.
2. Rasch DK, *et al.* Neurobehavioral effects of neonatal hypermagnesemia. *J Pediatr* 1982; 100: 272–6.
3. Atkinson MW, *et al.* The relation between magnesium sulfate therapy and fetal heart rate variability. *Obstet Gynecol* 1994; 83: 967–70.
4. Hallak M, *et al.* The effect of magnesium sulfate on fetal heart rate parameters: a randomized, placebo-controlled trial. *Am J Obstet Gynecol* 1999; 181: 1122–7.

Interactions

Parenteral magnesium sulfate potentiates the effects of competitive and depolarising neuromuscular blockers (p. 2033.2). The neuromuscular blocking effects of parenteral magnesium and aminoglycoside antibacterials may be additive. Similarly, parenteral magnesium sulfate and nifedipine have been reported to have additive effects (p. 1454.2).

Oral magnesium salts decrease the absorption of tetracyclines and bisphosphonates, and doses should be separated by a number of hours.

Pharmacokinetics

About one-third of magnesium is absorbed from the small intestine after oral doses and even soluble magnesium salts are generally very slowly absorbed. The fraction of magnesium absorbed increases if magnesium intake decreases. In plasma, about 25 to 30% of magnesium is protein bound. Parenteral magnesium salts are excreted mainly in the urine, and oral doses are eliminated in the urine (absorbed fraction) and the faeces (unabsorbed fraction). Small amounts are distributed into breast milk. Magnesium crosses the placenta.

Human Requirements

Magnesium is the second most abundant cation in intracellular fluid and is an essential body electrolyte which is a cofactor in numerous enzyme systems.

The body is very efficient at maintaining magnesium concentrations by regulating absorption and renal excretion, and symptoms of deficiency are rare. It is therefore difficult to establish a daily requirement.

Foods rich in magnesium include nuts, unmilled grains, and green vegetables.

UK and US recommended dietary intake. In the United Kingdom dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] and in the United States recommended daily allowances (RDA)[2] have been published for magnesium. In the UK the estimated average requirement (EAR) is 200 mg (or 8.2 mmol) daily for adult females and 250 mg (or 10.3 mmol) daily for adult males; the reference nutrient intake (RNI) is 270 mg (or 10.9 mmol) daily for adult females and 300 mg (or 12.3 mmol) daily for adult males; no increment is recommended during pregnancy but an increment of 50 mg (or 2.1 mmol) daily in the RNI is advised during lactation. In the USA under the new dietary reference intakes an EAR of 330 to 350 mg daily has been set in adult males and 255 to 265 mg daily in adult females; the corresponding RDAs are 400 to 420 mg and 310 to 320 mg daily.[2] An increase in RDA to 350 to 360 mg is recommended during pregnancy but the standard RDA is considered adequate during lactation. A tolerable upper intake level of 350 mg daily has been set for adults.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO. 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press. 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Biomag; Magnebe; Magnesio Vital; Total Magnesiano; *Austral.*: Celloids MP 65†; Magmin†; *Austria*: Cormagnesin; Emgecard; FX Passage; Magnesiocard; Magnesium Verla; Magnesium Verla; Magvital†; *Belg.*: Magnespasmyl; Ultra-Mg; *Braz.*: Magnoston; Pidomag; Sal Amargo Purificado†; *Canad.*: Epsom; Maglucate; Magnogene†; Magnonat†; Pansement Mag†; Proflavanol C†; Spasmag†; *Chile*: Mag-Tab; *China*: Bao Le (包乐); Panangin (福南金); Tian Jia Yuan (天甲元); *Cz.*: Magnerot; *Fin.*: Selutrio; *Fr.*: Efimag†; Mag 2; Maginjectable; Magnespasmyl; Magnogene; Megamag; Spasmag; Top-Mag†; *Ger.*: Basti-Mag; Cormagnesin; FX Passage; Magium†; Magnaspart; Magnerot A; magnerot Classic; Magnerot; Magnesiocard; Magnesium Diasporal; Magnesium Verla N; Magnesium Verla N; Magnesium Verla; Magnesium Verla; Magnesium Verla; Magnesium-Sandoz forte†; Magnesium-Sandoz†; Magnesorot; Mg 5-Longoral; Mg 5-Sulfat; Mgnor; Power Orot†; Retterspitz Darmreinigungspulver ST; *Gr.*: Mag 2; Solumag; Trofocard; Ultra-Mg; *Hong Kong*: Paulding Remedies Epsom Salts†; *Hung.*: Cormagnesin; Magnerot; Magnesiocard†; *India*: Mag; Magneon; *Irl.*: Magnesium Verla; *Ital.*: Mag 2; MG 50; Solumag; *Mex.*: Ifupeptol Magnesiado; *Mon.*: Oromag; *Norw.*: Nycoplus Magnesium; *Pol.*: Asmag; Biomag†; Laktomag B$_6$; Laktomag; *Magnefar*; *Slow-Mag*; *Port.*: Extraneal; Magnesiocard; Magnesona; Magnespasmil; Magnoral; Metabol-Mg; *Rus.*: Cormagnesin (Кормагнезин); Magnerot (Магнерот); Vita-Iodurol (Вита-иодурол); *S.Afr.*: Be-Lax; Mag SR; Magnesit; SB Laxative Mixture†; Slow-Mag; *Spain*: Actimag; Magnesioboi; *Switz.*: Actimagon†; Mag 2; Mag-Min†; Magnegon; Magnesiocard; Magnesium Biomed; Magnesium Biomed; Magnesium Vital; Magnesium-Sandoz; Mg 5-Granoral; Mg 5-Longoral; Mg 5-Oraleff; Solmag†; *Thal.*: Magfifty; Maglax; *Turk.*: Magnesiocard; *UK*: Kest; Magnaphate; Magnaspartate; *Ukr.*: Cormagnesin (Кормагнезин); Magnerot (Магнерот); *USA*: Chloromag; Mag-G; Mag-SR; Mag-Tab; Maginex; Magtrate; Slow-Mag.

Multi-ingredient Preparations. Numerous preparations are listed in Volume B.

Homoeopathic Preparations. *Austral.*: Colic Relief; Nervatona Focus; *Austria*: Osanit Zahnungskugelchen; *Canad.*: Biochemic Phosphates; Biomag†; Calms Forte; Col 138†; Combinaison†; Diamite; Ervopax†; Fibromyalgie; Formula C Doroon†; Formula FA 224†; Formula PC 223†; Homeo-Form T†; Hylands Bioplasma; Hylands Formula CP; Hylands Formula MC; Hylands Formula NT; Hylands LCQ; Hylands Leg Cramps; Hylands Menstrual Cramps†; Ikoplex 14†; Ikoplex 5†; Kid's Colic; Leg Cramps with Quinine; Melange†; Minerals+; Nerve Tonic; Nuage Bioplasma†; Passiflora Complex†; Rexorubia†; Spa Complex†; Spascupreel; Ton 1 Complex†; *Chile*: Ikoplex No 10; Ikoplex No 14; Ikoplex No 1; Ikoplex No 20; Ikoplex No 23; Ikoplex No 3; Ikoplex No 4; Ikoplex No 5; Ikoplex No 6; Ikoplex No 9; Lumboplex; *Cz.*: Spascupreel 5†; *Fr.*: Aloe Compose; Bilinum Complexe No 113; Biomag; Boripharm No 11†; Boripharm No 12†; Chelidonium Compose; Hepatocynesine†; L 25; Nervopax; Passiflora Compose; Rexorubia; Silicea Complexe No 11; Sulfur Complexe No 12; *Ger.*: Carminativum Hevert; Disci Bamb; Disco-cyl Ho-Len-Complex; Dolo-Injektopas; Drufusan N†; Drufusan; Dysmenorrhoe-Gastreu S R75; Femin-Do; Gastro Magentabletten; Girheulit HM†; Homviohepan; Infi-China; Lithias-cyl L Ho-Len-Complex; NeyArthros-Liposome (Revitorgan Lp Nr 83)†; NeyArthrosome (Revitorgan-Dilution)†; Osanit; Pectapas SL; Refesan T; Rufebran neuro†; Spascupreel; Spasmoject P; Spasmosyx P; Zitronensaurezyklus-Heel; *Hung.*: Spascupreel; *Neth.*: Co-Hypert; Kind 0-3 Cinababy; Spascupreel H; *Rus.*: Menalgin (Менальгин); *UK*: Medicinal Gargle; New Era Elasto; New Era Nervone; *Ukr.*: Enterocind (Энтероцинд).

Pharmacopoeial Preparations

BP 2014: Chewable Magnesium Glycerophosphate Tablets; Magnesium Chloride Injection; Magnesium Glycerophosphate Oral Solution; Magnesium Sulphate Injection; Magnesium Sulphate Mixture; Magnesium Sulphate Paste;

USP 36: Calcium and Vitamin D with Minerals Tablets; Magnesium Gluconate Tablets; Magnesium Sulfate in Dextrose Injection; Magnesium Sulfate Injection; Minerals Capsules; Minerals Tablets; Multiple Electrolytes and Dextrose Injection Type 1; Multiple Electrolytes and Dextrose Injection Type 2; Multiple Electrolytes and Dextrose Injection Type 4; Multiple Electrolytes and Invert Sugar Injection Type 1; Multiple Electrolytes and Invert Sugar Injection Type 2; Multiple Electrolytes Injection Type 1; Multiple Electrolytes Injection Type 2; Oil- and Water-soluble Vitamins with Minerals Capsules; Oil- and Water-soluble Vitamins with Minerals Oral Solution; Oil- and Water-soluble Vitamins with Minerals Tablets; Oil-Soluble Vitamins with Minerals Capsules; Oil-Soluble Vitamins with Minerals Oral Solution; Oil-Soluble Vitamins with Minerals Tablets; Water-soluble Vitamins with Minerals Capsules; Water-soluble Vitamins with Minerals Tablets.

Phosphate

Fosfato; Фосфат.

UNII — NK08V8K8HR.

Description. Phosphate is an anion given as various potassium or sodium salts.

Incompatibility. Phosphates are incompatible with calcium salts; the mixing of calcium and phosphate salts can lead to the formation of insoluble calcium-phosphate precipitates. Incompatibility has also been reported with magnesium salts.

Monobasic Potassium Phosphate

Dihydrogenfosforečnan draselný; E340; Fosfato monobásico de potasio; Kalii Dihydrogenophosphas; Kalio-divanderiilio fosfatas; Kálium-dihidrogén-foszfát; Kaliumdihydrogenphosphat; Kaliumdivätefosfat; Kaliumdivetyfosfaatti; Monopotassium Phosphate; Phosphate monopotassique; Potasio, dihidrogenofosfato de; Potassium Acid Phosphate; Potassium Biphosphate; Potassium Dihydrogen Phosphate; Potasu, diwodorofosforan; Ортофосфат Калия Однозамещенный.

Potassium dihydrogen orthophosphate.

KH_2PO_4=136.1

CAS — 7778-77-0.

UNII — 4J9FJ0HL51.

Pharmacopoeias. In *Eur.* (see p. vii). Also in *USNF*.

Ph. Eur. 8: (Potassium Dihydrogen Phosphate). A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; practically insoluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

USNF 31: (Monobasic Potassium Phosphate). Colourless crystals or a white granular or crystalline powder. Is odourless. Freely soluble in water; practically insoluble in

alcohol. pH of a 1% solution in water is about 4.5. Store in airtight containers.

Equivalence. Each g of monobasic potassium phosphate represents about 7.3 mmol of potassium and of phosphate.

Dibasic Potassium Phosphate

Dikalii Phosphas; Dikalio fosfatas; Dikaliumfosfaatti; Dikaliumfosfat; Dikálium-hidrogén-foszfát; Dipotasio, hidrogenofosfato de; Dipotassium Hydrogen Phosphate; Dipotassium Phosphate; Dipotasu wodorofosforan; E340; Fosfato dibásico de potasio; Hydrogenfosforečnan draselný; Kalii Hydrogenophosphas; Kaliummonohydrogenphosphat; Phosphate dipotassique; Potassium Phosphate; Ортофосфат Калия Двузамещенный.

Dipotassium hydrogen orthophosphate.

K_2HPO_4=174.2

CAS — 7758-11-4.

UNII — B7862WZ632 (potassium phosphate); CI71S98N1Z (dibasic potassium phosphate).

Pharmacopoeias. In *Eur.* (see p. vii) and *US.*

Ph. Eur. 8: (Dipotassium Phosphate; Dipotassium Hydrogen Phosphate BP 2014). A very hygroscopic, white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. Store in airtight containers.

USP 36: (Dibasic Potassium Phosphate). Colourless or white, somewhat hygroscopic, granular powder. Freely soluble in water; very slightly soluble in alcohol. pH of a 5% solution in water is between 8.5 and 9.6.

Equivalence. Each g of dibasic potassium phosphate represents about 11.5 mmol of potassium and 5.7 mmol of phosphate.

Monobasic Sodium Phosphate

Dihydrogenfosforečnan sodný; E339; Fosfato monobásico de sodio; Monobazik Sodyum Fosfat; Natrii Dihydrogenophosphas; Natrio-divandenilo fosfatas; Natrium Phosphoricum Monobasicum; Nátrium-dihidrogén-foszfát; Natriumdivätefosfat; Natriumdivetyfosfaatti; Phosphate monosodique; Sodio, dihidrogenofosfato de; Sodium Acid Phosphate; Sodium Biphosphate; Sodium Dihydrogen Phosphate; Sodu diwodorofosforan; Sodyum Dihidrojen Fosfat; Ортофосфат Натрия Однозамещенный.

Sodium dihydrogen orthophosphate.

$NaH_2PO_4xH_2O$

CAS — 7558-80-7 (anhydrous monobasic sodium phosphate); 10049-21-5 (monobasic sodium phosphate monohydrate); 13472-35-0 (monobasic sodium phosphate dihydrate).

ATC — A06AD17; A06AG01.

ATC Vet — QA06AD17; QA06AG01.

UNII — 3980JIH2SW (monobasic sodium phosphate); KH7I04HPUU (anhydrous monobasic sodium phosphate); 593YOG76RN (monobasic sodium phosphate monohydrate); 5QWK665956 (monobasic sodium phosphate dihydrate).

Pharmacopoeias. *Br., Chin., Eur.* (see p. vii), and *US* may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (NaH_2PO_4 = 120.0), the monohydrate ($NaH_2PO_4.H_2O$ = 138.0), and the dihydrate ($NaH_2PO_4.2H_2O$ = 156.0), although not necessarily all will be found in any one pharmacopoeia.

Ph. Eur. 8: (Sodium Dihydrogen Phosphate Dihydrate; Natrii Dihydrogenophosphas Dihydricus). A white or almost white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

The BP 2014 gives Sodium Acid Phosphate as an approved synonym.

BP 2014: (Anhydrous Sodium Dihydrogen Phosphate). A white, slightly deliquescent, crystals or granules. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

BP 2014: (Sodium Dihydrogen Phosphate Monohydrate). A white powder or colourless crystals. Very soluble in water; very slightly soluble in alcohol. A 5% solution in water has a pH of 4.2 to 4.5.

USP 36: (Monobasic Sodium Phosphate). It contains one or two molecules of water of hydration, or is anhydrous. Colourless crystals or white crystalline powder. Is odourless and is slightly deliquescent. Freely soluble in water; practically insoluble in alcohol. Its solutions are acid to litmus and effervesce with sodium carbonate. pH of a 5% solution in water of the monohydrate form is between 4.1 and 4.5.

Equivalence. Each g of monobasic sodium phosphate (anhydrous) represents about 8.3 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (monohydrate) represents about 7.2 mmol of sodium and of phosphate. Each g of monobasic sodium phosphate (dihydrate) represents about 6.4 mmol of sodium and of phosphate.

Dibasic Sodium Phosphate

Dibazik Sodyum Hidrojen Fosfat; Dinatrii Phosphas; Dinatrio fosfatas; Dinatriumfosfaatti; Dinatriumfosfat; Dinátrium-hidrogén-foszfát; Disodio, hidrogenofosfato de; Disodium Hydrogen Phosphate; Disodium Phosphate; Disodu fosforan; Disodu wodorofosforan; Disodyum Hidrojen Fosfat; E339; Fosfato dibásico de sodio; Hydrogenfosforečnan sodný; Natrii Hydrogenophosphas; Natrii Phosphas; Natrii Phosphatis; Natriumfosfaatti; Natriumfosfat; Phosphate disodique; Sodium Phosphate; Ортофосфат Натрия Двузамещенный.

Disodium hydrogen orthophosphate.

$Na_2HPO_4xH_2O$

CAS — 7558-79-4 (anhydrous dibasic sodium phosphate); 10028-24-7 (dibasic sodium phosphate dihydrate); 7782-85-6 (dibasic sodium phosphate heptahydrate); 10039-32-4 (dibasic sodium phosphate dodecahydrate).

ATC — A06AD17; A06AG01; B05XA09.

ATC Vet — QA06AD17; QA06AG01; QB05XA09.

UNII — SE337SVY37 (sodium phosphate); GR686LBA74 (dibasic sodium phosphate); 22ADO53M6F (anhydrous dibasic sodium phosphate); 94255I6E2T (dibasic sodium phosphate dihydrate); 70WT22SF4B (dibasic sodium phosphate heptahydrate); E1W4N241FO (dibasic sodium phosphate dodecahydrate).

Pharmacopoeias. In *Eur.* (see p. vii), *Jpn*, and *US*. The pharmacopoeias may specify one or more states of hydration; monographs and specifications can be found for the anhydrous form (Na_2HPO_4 = 142.0), the dihydrate ($Na_2HPO_4.2H_2O$ = 178.0), the heptahydrate ($Na_2HPO_4.7H_2O$ = 268.1), and the dodecahydrate ($Na_2HPO_4.12H_2O$ = 358.1), although not necessarily all will be found in any one pharmacopoeia.

Ph. Eur. 8: (Disodium Phosphate, Anhydrous; Dinatrii Phosphas Anhydricus; Anhydrous Disodium Hydrogen Phosphate BP 2014). A white or almost white, hygroscopic powder. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline. Store in airtight containers.

Ph. Eur. 8: (Disodium Phosphate Dihydrate; Dinatrii Phosphas Dihydricus; Disodium Hydrogen Phosphate Dihydrate BP 2014). A white or almost white powder or colourless crystals. Soluble in water; practically insoluble in alcohol. A 5% solution in water is slightly alkaline.

The BP 2014 gives Sodium Phosphate Dihydrate as an approved synonym.

Ph. Eur. 8: (Disodium Phosphate Dodecahydrate; Dinatrii Phosphas Dodecahydricus; Disodium Hydrogen Phosphate Dodecahydrate BP 2014). Colourless, transparent, very efflorescent crystals. Very soluble in water; practically insoluble in alcohol. A 10% solution in water is slightly alkaline.

USP 36: (Dibasic Sodium Phosphate). It is dried, or contains one, two, seven, or twelve molecules of water of hydration. The dried substance is a white powder that readily absorbs moisture. It is soluble 1 in 8 of water; insoluble in alcohol. The heptahydrate is a colourless or white, granular or caked salt that effloresces in warm, dry air. It is freely soluble in water; very slightly soluble in alcohol. Its solutions are alkaline to phenolphthalein, a 0.1M solution having a pH of about 9.

Store all forms in airtight containers.

Equivalence. Each g of dibasic sodium phosphate (anhydrous) represents about 14.1 mmol of sodium and 7.0 mmol of phosphate. Each g of dibasic sodium phosphate (dihydrate) represents about 11.2 mmol of sodium and 5.6 mmol of phosphate. Each g of dibasic sodium phosphate (heptahydrate) represents about 7.5 mmol of sodium and 3.7 mmol of phosphate. Each g of dibasic sodium phosphate (dodecahydrate) represents about 5.6 mmol of sodium and 2.8 mmol of phosphate.

Tribasic Sodium Phosphate

E339; Fosfato de trisodio; Ortofosfato de trisodio; Sodio, fosfato de; Trisodium Orthophosphate; Trisodium Phosphate; Ортофосфат Натрия Трехзамещенный.

Na_3PO_4=163.9

CAS — 7601-54-9.

ATC — A06AD17; A06AG01.

ATC Vet — QA06AD17; QA06AG01.

UNII — A752Q30A6X (tribasic sodium phosphate); SX01TZO3QZ (anhydrous tribasic sodium phosphate); J9O85FKF29 (tribasic sodium phosphate monohydrate); B70850QPHR (tribasic sodium phosphate dodecahydrate).

Pharmacopoeias. In *USNF.*

USNF 31: (Tribasic Sodium Phosphate). It is anhydrous or contains 1 to 12 molecules of water of hydration. White, odourless crystals or granules, or a crystalline powder. Freely soluble in water; insoluble in alcohol. pH of a 1% solution in water is between 11.5 and 12.0. Store in airtight containers.

Equivalence. Each g of tribasic sodium phosphate (anhydrous) represents about 18.3 mmol of sodium and 6.1 mmol of phosphate.

Uses and Administration

Phosphates are used in the management of **hypophosphataemia** caused by phosphate deficiency or hypophosphataemic states (p. 1777.1). Doses of up to 100 mmol of phosphate daily may be given orally. The intravenous route is seldom necessary, but a dose of up to 9 mmol of phosphate as monobasic potassium phosphate may be given over 12 hours and repeated every 12 hours as necessary for severe hypophosphataemia. Alternatively, 0.2 to 0.5 mmol/kg phosphate, up to a maximum of 50 mmol, may be given over 6 to 12 hours (see also Hypophosphataemia, below). Plasma-electrolyte concentrations, especially phosphate and calcium, and renal function should be carefully monitored. Reduced doses may be necessary in patients with renal impairment. Phosphate supplements are used in total parenteral nutrition regimens; typical daily requirements are 20 to 30 mmol of phosphate.

Phosphates act as mild osmotic **laxatives** (p. 1804.1) when given orally as dilute solutions or by the rectal route. Phosphate enemas or concentrated oral solutions are used for bowel cleansing before surgery or endoscopy procedures. Preparations typically combine monobasic and dibasic sodium phosphates but the composition and dosage do vary slightly. Phosphate enemas act within 2 to 5 minutes, whereas the oral solutions act within 30 minutes to 6 hours.

Phosphates also have **other uses**. They lower the pH of urine and have been given as adjuncts to urinary antibacterials that depend on an acid urine for their activity. Phosphates have also been used for the prophylaxis of calcium renal calculi; the phosphates reduce urinary excretion of calcium thus preventing calcium deposition. A suggested oral dose for both uses is 7.4 mmol of phosphate four times daily.

Butafosfan (1-butylamino-1-methylethylphosphinic acid) and the sodium salt of toldimfos (4-dimethylamino-*O*-tolylphosphinic acid) are used as phosphorus sources in veterinary medicine.

Administration in children. For doses of phosphate to be used in children to treat vitamin-D-resistant rickets and rickets of prematurity, see p. 1792.1.

Bowel evacuation. A review concluded that the efficacy and tolerability of oral sodium phosphate solution was generally similar to, or significantly better than, that of polyethylene glycol-based or other colorectal cleansers in patients preparing for colorectal-related procedures.[1]

1. Curran MP, Plosker GL. Oral sodium phosphate solution: a review of its use as a colorectal cleanser. *Drugs* 2004; 64: 1697–1714.

Hypercalcaemia. Intravenous phosphates have been used to lower plasma-calcium concentrations in hypercalcaemic emergencies (p. 1776.1), but because of their potential to cause serious adverse effects other drugs are now preferred. Oral phosphates may be used to prevent gastrointestinal absorption of calcium in the treatment of hypercalcaemia. The dose in adults is up to 100 mmol phosphate daily adjusted according to response.

Hypophosphataemia. Phosphate salts are given in the management of hypophosphataemia when a phosphate deficiency is identified, as discussed in Uses and Administration, above. Intravenous phosphates are associated with serious adverse effects if hypophosphataemia is over-corrected, and the rise in serum-phosphorus concentration cannot be predicted from a given dose. Consequently, it has been recommended[1-4] that intravenous phosphate be used cautiously in the treatment of severe hypophosphataemia (for the standard rate and dose see Uses and Administration, above). However, some advocate a more aggressive fixed-dose regimen in critically ill patients.[5-7]

1. Vannatta JB, *et al.* Efficacy of intravenous phosphorus therapy in the severely hypophosphataemic patient. *Arch Intern Med* 1981; 141: 885–7.
2. Anonymous. Treatment of severe hypophosphatemia. *Lancet* 1981; ii: 734.
3. Lloyd CW, Johnson CE. Management of hypophosphatemia. *Clin Pharm* 1988; 7: 123–8.
4. Coyle S, *et al.* Treatment of hypophosphataemia. *Lancet* 1992; 340: 977.
5. Perreault MM, *et al.* Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Ann Pharmacother* 1997; 31: 683–8.

6. Miller DW, Slovis CM. Hypophosphatemia in the emergency department therapeutics. *Am J Emerg Med* 2000; 18: 457–61.
7. Charron T, *et al.* Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphatemia. *Intensive Care Med* 2003; 29: 1273–8.

Osteomalacia. Vitamin D deficiency, or its abnormal metabolism, is the most usual cause of osteomalacia and rickets (p. 1168.1); however, phosphate depletion may also contribute, and phosphate supplementation may be given as appropriate.

A suggested oral dose for vitamin-D-resistant hypophosphataemic osteomalacia in adults is 65 to 100 mmol phosphate daily. The *BNFC* suggests the following oral phosphate doses:

- for neonates, 1 mmol/kg daily given as a single dose or in 2 divided doses; alternatively it may be given via fortified breast milk
- older children may be given 2 to 3 mmol/kg daily, in 2 to 4 divided doses; a maximum dose of 48 mmol daily is recommended in those up to 5 years of age, and a maximum of 97 mmol daily for those aged 5 years and over.

If parenteral administration is indicated, an intravenous infusion of 1 mmol/kg daily may be given to neonates, 0.7 mmol/kg daily to children aged 1 month to 2 years, and 0.4 mmol/kg daily to those aged 2 to 18 years. Doses should be adjusted as necessary.

RICKETS OF PREMATURITY. Dietary deficiency of phosphorus is unusual, but can occur in small premature infants fed exclusively on human breast milk. The phosphate intake in these infants appears to be inadequate to meet the needs of bone mineralisation, and hypophosphataemic rickets can develop. This condition, variably called metabolic bone disease of prematurity, or rickets of prematurity, can be prevented by ensuring an adequate phosphate intake by very low-birth-weight babies. Adequate intake of calcium and vitamin D is also essential. Phosphate supplementation, with calcium and vitamin D, may be given orally either in formula feeds or as fortification of human breast milk, or intravenously in parenteral nutrition solutions.[1,2]

Dosage recommendations for phosphate may vary, but the *BNFC* suggests a daily dose of 1 mmol/kg; if given orally, this may be as a single dose or in 2 divided doses.

1. Ryan S. Nutritional aspects of metabolic bone disease in the newborn. *Arch Dis Child Fetal Neonatal Ed* 1996; 74: F145–8.
2. Harrison CM, *et al.* Osteopenia of prematurity: a national survey and review of practice. *Acta Paediatr* 2008; 97: 407–13.

Adverse Effects and Treatment

Excessive doses of intravenous phosphate cause hyperphosphataemia, particularly in patients with renal failure. Hyperphosphataemia leads in turn to hypocalcaemia, which may be severe, and to ectopic calcification, particularly in patients with initial hypercalcaemia. Tissue calcification may cause hypotension and organ damage and result in acute renal failure. Hyperphosphataemia, hypocalcaemia, and tissue calcification are rare after oral or rectal doses (but see Effects on Electrolytes, and Effects on the Kidneys, below).

Adverse effects of oral phosphates may include nausea, vomiting, diarrhoea, and abdominal pain. When they are being used for indications other than their laxative effects, diarrhoea may necessitate a reduction in dosage. Sodium phosphates given rectally for bowel evacuation may cause local irritation.

Phosphates are given as the potassium or sodium salts or both, and may thus be associated with hyperkalaemia, and hypernatraemia and dehydration. Sodium phosphate may cause hypokalaemia.

Treatment of adverse effects involves withdrawal of phosphate, general supportive measures, and correction of serum-electrolyte concentrations, especially calcium. Measures to remove excess phosphate such as oral phosphate binders and haemodialysis may be required (see also Hyperphosphataemia, p. 1776.3).

Effects on electrolytes. Although less common than after intravenous therapy, hyperphosphataemia, accompanied by hypocalcaemia or other severe electrolyte disturbances and resulting in tetany[1,2] and even death,[2] has been reported after the use of phosphate enemas. Similar effects have also been reported with the use of oral phosphate laxatives,[3–7] and in the USA, the FDA has issued warnings of the risk of electrolyte disturbances after the use of high oral doses of sodium phosphate, particularly in vulnerable patients.[8] Infants or children,[2,9,10] the elderly,[4,11] and those with renal impairment,[1,4,11] or congestive heart failure[4] have often had these adverse effects. Licensed product information for one oral sodium phosphate bowel cleanser (*Visicol; Salix, USA*) states that there have been reports of generalised tonic-clonic seizures and/or loss of consciousness in patients with no history of seizures; these cases were associated with electrolyte abnormalities, and low serum osmolality.

Hyperphosphataemia may precipitate nephrocalcinosis, causing an acute phosphate nephropathy, see Effects on the Kidneys, below.

1. Haskell LP. Hypocalcaemic tetany induced by hypertonic-phosphate enema. *Lancet* 1985; ii: 1433.
2. Martin RR, *et al.* Fatal poisoning from sodium phosphate enema: case report and experimental study. *JAMA* 1987; 257: 2190–2.
3. Peixoto Filho AJ, Lassman MN. Severe hyperphosphatemia induced by a phosphate-containing oral laxative. *Ann Pharmacother* 1996; 30: 141–3.
4. Adverse Drug Reactions Advisory Committee (ADRAC). Electrolyte disturbances with oral phosphate bowel preparations. *Aust Adverse Drug React Bull* 1997; 16: 2. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9702.htm (accessed 04/08/08)
5. Ullah N, *et al.* Fatal hyperphosphatemia from a phosphosoda bowel preparation. *J Clin Gastroenterol* 2002; 34: 457–8.
6. Woo YM, *et al.* A life threatening complication after ingestion of sodium phosphate bowel preparation. *BMJ* 2006; 333: 589–90.
7. Domico MB, *et al.* Severe hyperphosphatemia and hypocalcemic tetany after oral laxative administration in a 3-month-old infant. *Pediatrics* 2006; 118: e1580–e1583. Also available at: http://pediatrics.aappublications.org/cgi/reprint/118/5/e1580 (accessed 13/12/06)
8. FDA. Safety of Sodium Phosphates Oral Solution (Issued 17th September, 2001). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm173897.htm (accessed 20/08/10)
9. McCabe M, *et al.* Phosphate enemas in childhood: cause for concern. *BMJ* 1991; 302: 1074.
10. Harrington L, Schuh S. Complications of Fleet enema administration and suggested guidelines for use in the pediatric emergency department. *Pediatr Emerg Care* 1997; 13: 225–6.
11. Boivin MA, Kahn SR. Symptomatic hypocalcemia from oral sodium phosphate: a report of two cases. *Am J Gastroenterol* 1998; 93: 2577–9.

Effects on the kidneys. Acute renal failure and nephrocalcinosis have been reported after the use of oral phosphate-based cathartics for bowel cleansing.[1,2] Although relatively rare with oral preparations, this acute phosphate nephropathy is a serious adverse effect; most patients were left with chronic renal insufficiency, and some developed end-stage renal disease. Potential contributing factors include inadequate hydration, increased age, a history of hypertension and arteriosclerosis, and concurrent use of ACE inhibitors, angiotensin receptor antagonists, diuretics, or NSAIDs.[2] The FDA has issued warnings[3] about the use of oral sodium phosphate products, especially in patients with impaired renal function, hypovolaemia, decreased intravascular volume, or dehydration, or in those taking drugs likely to contribute to the risk of nephropathy. Patients with bowel obstruction or active colitis may also be at risk. Patient advice includes the need to take the correct dose of oral sodium phosphate, to drink sufficient liquid during bowel cleansing, and to avoid other phosphate-containing laxatives. Patients at increased risk should have their electrolytes and renal function monitored.

Nephrocalcinosis has also been reported in children with hypophosphataemic rickets treated with calcitriol and phosphate supplements; this was found to be associated with the phosphate dose.[4]

1. Desmeules S, *et al.* Acute phosphate nephropathy and renal failure. *N Engl J Med* 2003; 349: 1006–7.
2. Markowitz GS, *et al.* Acute phosphate nephropathy following oral sodium phosphate bowel purgative: an underrecognized cause of chronic renal failure. *J Am Soc Nephrol* 2005; 16: 3389–96.
3. FDA. Oral sodium phosphate (OSP) products for bowel cleansing (marketed as Visicol and OsmoPrep, and oral sodium phosphate products available without a prescription) (issued 12th November, 2008). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103354.htm (accessed 20/08/10)
4. Verge CF, *et al.* Effects of therapy in X-linked hypophosphatemic rickets. *N Engl J Med* 1991; 325: 1843–8.

Local toxicity. Rectal gangrene has been associated with the use of phosphate enemas in elderly patients and was believed to be due to a direct necrotising effect of the phosphate on the rectum.[1]

1. Sweeney JL, *et al.* Rectal gangrene: a complication of phosphate enema. *Med J Aust* 1986; 144: 374–5.

Precautions

Phosphates should not generally be given to patients with severe renal impairment. They should be avoided in patients who may have low serum-calcium concentrations, as these may decrease further, and in patients with infected phosphate renal calculi. Potassium phosphates should be avoided in patients with hyperkalaemia and sodium phosphates should generally be avoided in patients with congestive heart failure, hypertension, and oedema. Serum electrolytes and renal function should be monitored during therapy, particularly if phosphates are given parenterally.

Oral or rectal sodium phosphate preparations for bowel evacuation should not be used in patients with gastrointestinal obstruction, inflammatory bowel disease, and conditions where there is likely to be increased colonic absorption. They should be used cautiously in elderly and debilitated patients, and in those with pre-existing electrolyte disturbances (see Effects on Electrolytes, above).

Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAPOS) and the Porphyria Centre Sweden, classifies potassium and sodium phosphates as not porphyrinogenic; they may be used as drugs of first choice and no precautions are needed.[1]

1. The Drug Database for Acute Porphyria. Available at: http://www.drugs-porphyria.org (accessed 26/10/11)

Interactions

Oral phosphate supplements should not be used with aluminium, calcium, or magnesium salts as these will bind phosphate and reduce its absorption. Vitamin D increases the gastrointestinal absorption of phosphates and therefore increases the potential for hyperphosphataemia.

Hyperphosphataemia, hypocalcaemia, and hypernatraemia are more likely to occur with phosphate enemas or oral laxatives if these are given to patients receiving diuretics or other drugs that may affect serum electrolytes. The risk of ectopic calcification may be increased by concurrent use of calcium supplements or calcium-containing antacids.

The risk of hyperkalaemia is increased if potassium phosphates are given with drugs that can increase serum-potassium concentrations.

Pharmacokinetics

About two-thirds of ingested phosphate is absorbed from the gastrointestinal tract. Excess phosphate is mainly excreted in the urine, the remainder being excreted in the faeces.

References.

1. Larson JE, *et al.* Laxative phosphate poisoning: pharmacokinetics of serum phosphorus. *Hum Toxicol* 1986; 5: 45–9.

Human Requirements

Phosphorus requirements are usually regarded as equal to those of calcium.

Most foods contain adequate amounts of phosphate, particularly meat and dairy products, hence deficiency is virtually unknown except in certain disease states, in patients receiving total parenteral nutrition, or in those who have received phosphate-binding drugs for prolonged periods; for further details see under Hypophosphataemia, p. 1777.1.

UK and US recommended dietary intake. In the UK dietary reference values (DRV—see Human Requirements, p. 2046.1)[1] and in the USA dietary reference intakes including recommended dietary allowances (RDA)[2] have been published for phosphorus. In the UK the reference nutrient intake (RNI) for adults is about 550 mg (17.5 mmol) daily; no additional amount is recommended for pregnancy although an additional amount of about 440 mg (14.3 mmol) daily is advised during lactation. In the USA the RDA is 1250 mg daily for those aged 9 to 18 years and 700 mg daily in adults; no increase in RDA is recommended during pregnancy and lactation. A tolerable upper intake level of 4 g daily has been set in adults aged up to 70 years; in those older than 70 a maximum of 3 g daily is recommended.[2]

1. DoH. Dietary reference values for food energy and nutrients for the United Kingdom: report of the panel on dietary reference values of the committee on medical aspects of food policy. *Report on health and social subjects 41*. London: HMSO, 1991.
2. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes of the Food and Nutrition Board. *Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride*. Washington, DC: National Academy Press, 1999. Also available at: http://www.nap.edu/openbook.php?isbn=0309063507 (accessed 21/07/08)

Preparations

Proprietary Preparations (details are given in Volume B)

Single-ingredient Preparations. *Arg.*: Denverlax; Dicofan; Enemol; Fosfacol; Fosfafarma†; Fosfalax; Fosfo-Dom; Fosfoadital; Fosfobarigraf; Gadolax; Kritel Enema; Prontonema; Sliaxa; Tekfema; *Austral.*: Celloids PP 85†; Celloids SP 96†; Diacol; Fleet Phospho-Soda; Fleet Ready-to-Use; Phosphate-Sandoz; Phosphoprep†; *Austria*: Fleet Phospho-Soda; Relaxyl†; *Belg.*: Colexklysma; Fleet Enema; Fleet Phospho-Soda; Kaliphos; Sodiphos; *Braz.*: Fleet Enema; Phosfoenema; *Canad.*: Enema; Fleet Enema; Phoslax; Phosphates; Relieve†; *Chile*: Fabulaxol; Fleet Enema; Fleet Fosfosoda; *China*: Fleet Enema (辉力); Fleet Phospho-Soda (辉灵); Gu Ping (固平); Qing Ke Long (清可隆); *Denm.*: Fleet; Phosphoral; *Fin.*: Phosphoral; *Fr.*: Colokit; Fleet Phospho-Soda; *Ger.*: Fleet Phospho-Soda; Freka-Clyss†; Isogutt†; *Gr.*: Bioklysm; Enema Cooper; Fleet Enema; Fleet Ready-to-Use; Fosfolax; Klysmol; *Hong Kong*: Enemol†; Fleet Enema; Fleet Phospho-Soda; Unima; *Hung.*: Fleet Phospho-Soda; Optacid; *India*: Exelyte; Exit; *Indon.*: Fleet Enema; Fleet Phosposoda; *Irl.*: Fleet Phospho-Soda; Fleet; *Israel*: Fleet Enema; *Malaysia*: Fleet Enema; Fleet Phospho-Soda; *Mex.*: Fleet Enema Fosf-Sodio; Fleet PS; *Neth.*: Fleet Gebruiksklaar Klysma†; Phosphoral; *Norw.*: Fleet Phospho-Soda; Phosphoral; *NZ*: Fleet Phosphate Enema; Fleet Phospho-Soda; *Philipp.*: Fleet Enema; Oksna†; Phospho-Soda; *Pol.*: Enema; Fleet Phospho-Soda; Phospho-Laxative†; Rectanal; *Port.*: Fleet Enema; Fleet Phospho-Soda; *Rus.*: Fleet Phospho-Soda (Флит Фосфосода); *Singapore*: Fleet Enema; Fleet Phospho-Soda; Phosphates; *Spain*: Fosfoevac; Fosfosoda; Lainema; *Swed.*: Phosphoral; *Switz.*: Freka-Clyss; *Thai.*: Patar 88 Enema; RISS;